ANTIBODIES TO C-MET FOR THE TREATMENT OF CANCERS

The present application claims priority under Title 35, United States Code, §119 to United States Provisional application Serial No. 60/447,073, filed February 13, 2003, which is incorporated by reference in its entirety as if written herein.

FIELD OF THE INVENTION

[001] This application relates to c-Met protein tyrosine kinase antibodies, particularly antagonists of HGF binding to c-Met. The application also relates to the use of the antibodies in therapy or diagnosis of particular pathological conditions in mammals, including cancer.

BACKGROUND OF THE INVENTION

[002] Hepatocyte growth factor (HGF) functions as a growth factor for particular tissues and cell types. HGF was identified initially as a mitogen for hepatocytes [Michalopoulos et al., *Cancer Res.*, 44:4414-4419 (1984); Russel et al., *J. Cell. Physiol.*, 119:183- 192 (1984); Nakamura et al., *Biochem. Biophys. Res. Comm.*, 122:1450-1459 (1984)]. Nakamura et al., *supra*, reported the purification of HGF from the serum of partially hepatectomized rats. Subsequently, HGF was purified from rat platelets, and its subunit structure was determined [Nakamura et al., *Proc. Natl. Acad. Sci. USA,* 83:6489-6493 (1986); Nakamura et al., *FEBS Letters,* 224:311-316 (1987)]. The purification of human HGF from human plasma was first described by Gohda et al., *J. Clin. Invest.*, 81:414-419 (1988).

[003] Both rat HGF and human HGF have been molecularly cloned, including the cloning and sequencing of a naturally occurring variant lacking 5 amino acids designated "delta5 HGF" [Miyazawa et al., *Biochem. Biophys. Res. Comm.*, 163:967-973 (1989); Nakamura et al., *Nature,* 342:440-443 (1989); Seki et al., *Biochem. Biophys. Res. Commun.* 172:321-327 (1990); Tashiro et al., *Proc. Natl. Acad. Sci. USA* , 87:3200-3204 (1990); Okajima et al., *Eur. J. Biochem* ., 193:375- 381 (1990)].

[004] The mature form of human HGF, corresponding to the major form purified from serum, is a disulfide-linked heterodimer derived by proteolytic cleavage of the pro-hormone between amino acids R494 and V495. This cleavage generates a molecule composed of an α-subunit of 440 amino acids (M_r 69 kDa) and a β-subunit of 234 amino acids (M_r 34 kDa). The nucleotide sequence of human HGF cDNA reveals that both the α-and the β-chains are contained in a single open reading frame coding for a pre-pro precursor protein. In the predicted primary structure of mature human HGF, an interchain disulfide bridge is formed between Cys 487 of the α-chain and Cys 604 in the β-chain [see Nakamura et al., *Nature, supra*]. The N-terminus of the α chain is preceded by 54 amino acids, starting with a methionine. This segment includes a characteristic hydrophobic leader (signal) sequence of 31 residues and the prosequence. The α-chain starts at amino acid (aa) 55, and contains four kringle domains. The kringle 1 domain extends from about aa 128 to about aa 206, the kringle 2 domain is between about aa 211 and about aa 288, the kringle 3 domain is defined as extending from about aa 303 to about aa 383, and the kringle 4 domain extends from about aa 391 to about aa 464 of the α-chain.

[005] The definition of the various kringle domains is based on their homology with kringle-like domains of other proteins (such as prothrombin and plasminogen); therefore, the above limits are only approximate. To date, the function of these kringles has not been determined. The β-chain of human HGF shows 38% homology to the catalytic domain of serine protease plasminogen. However, two of the three residues which form the catalytic triad of serine proteases requisite for enzymatic activity are not conserved in human HGF. Therefore, despite its serine protease-like domain, human HGF appears to have no proteolytic activity, and the precise role of the β-chain remains unknown. HGF contains four putative glycosylation sites, which are located at positions 294 and 402 of the α-chain and at positions 566 and 653 of the β-chain.

[006] In a portion of cDNA isolated from human leukocytes, in-frame deletion of 15 base pairs was observed. Transient expression of the cDNA sequence in COS-1 cells revealed that the encoded HGF molecule (delta5 HGF) lacking 5 amino acids in the kringle 1 domain was fully functional [Seki et al., *supra*].

[007] A naturally occurring human HGF variant has been identified which corresponds to an alternative spliced form of the transcript containing the coding

sequences for the N-terminal finger and first two kringle domains of mature HGF [Chan et al., *Science,* 254:1382- 1385 (1991); Miyazawa et al., *Eur. J. Biochem.* 197:15-22 (1991)]. This variant, designated HGF/NK2, has been proposed to be a competitive antagonist of mature HGF. Comparisons of the amino acid sequence of rat HGF with that of human HGF have revealed that the two sequences are highly conserved and have the same characteristic structural features. The length of the four kringle domains in rat HGF is exactly the same as in human HGF. Furthermore, the cysteine residues are located in exactly the same positions, an indication of similar three- dimensional structures [Okajima et al., *supra*; Tashiro et al., *supra*].

[008] HGF and HGF variants are described further in U.S. Pat. Nos. 5,227,158, 5,316,921, and 5,328,837.

[009] The HGF receptor has been identified as the product of the c-Met proto-oncogene [Bottaro et al., *Science,* 251:802-804 (1991); Naldini et al., *Oncogene,* 6:501-504 (1991); WO 92/13097 published Aug. 6, 1992; WO 93/15754 published Aug. 19, 1993]. The receptor is usually referred to as "c-Met" or "p190 ^{MET} " and typically comprises, in its native form, a 190-kDa heterodimeric (a disulfide-linked 50-kDa α-chain and a 145-kDa β-chain) membrane-spanning tyrosine kinase protein [Park et al., *Proc. Natl. Acad. Sci. USA,* 84:6379-6383 (1987)]. Several truncated forms of the c-Met receptor have also been described [WO 92/20792; Prat et al., *Mol. Cell. Biol.*, 11:5954- 5962 (1991)].

[0010] The binding activity of HGF to c-Met is believed to be conveyed by a functional domain located in the N-terminal portion of the HGF molecule, including the first two kringles [Matsumoto et al., *Biochem. Biophys. Res. Commun.* 181:691-699 (1991); Hartmann et al., *Proc. Natl. Acad. Sci* ., 89:11574-11578 (1992); Lokker et al., *EMBO J* ., 11:2503-2510 (1992); Lokker and Godowski, *J. Biol. Chem* ., 268:17145-117150 (1991)]. The c-Met protein tyrosine kinase becomes phosphorylated on several tyrosine residues of the 145-kDa β-subunit upon HGF binding.

[0011] Certain antibodies to HGF receptor have been reported in the literature. Several such antibodies are described below.

[0012] Prat et al., *Mol. Cell. Biol., supra,* describe several monoclonal antibodies specific for the extracellular domain of the β-chain encoded by the c-Met gene [see also, WO 92/20792]. The monoclonal antibodies were selected following

immunization of Balb/c mice with whole living GTL-16 cells (human gastric carcinoma cell line) overexpressing the c-Met protein. The spleen cells obtained from the immunized mice were fused with Ag8.653 myeloma cells, and hybrid supernatants were screened for binding to GTL-16 cells. Four monoclonal antibodies, referred to as DL-21, DN-30, DN-31, and DO-24, were selected.

[0013] Prat et al., *Int. J. Cancer,* 49:323-328 (1991) describe using c-Met monoclonal antibody DO-24 for detecting distribution of the c- Met protein in human normal and neoplastic tissues [see, also, Yamada et al., *Brain Research,* 637:308-312 (1994)]. The murine monoclonal antibody DO-24 was reported to be an IgG2a isotype antibody.

[0014] Crepaldi et al., *J. Cell Biol.*, 125: 313-320 (1994) report using monoclonal antibodies DO-24 and DN-30 [described in Prat et al., *Mol. Cell. Biol., supra*] and monoclonal antibody DQ-13 to delineate the subcellular distribution of c-Met in epithelial tissues and in MDCK cell monolayers. According to Crepaldi et al., monoclonal antibody DQ-13 was raised against a peptide corresponding to nineteen carboxy-terminal amino acids (from Ser ^{1372} to Ser $^{1390)}$ of the human c-Met sequence.

[0015] A monoclonal antibody specific for the cytoplasmic domain of human c-Met has also been described [Bottaro et al., *supra*].

[0016] Monovalent c-Met antibodies, including 1A3.3.13 antibody (ATCC deposit No. HB-11894) and 5D5.11.6 antibody (ATCC deposit No. HB-11895), and methods of treating cancers using such are disclosed in US 5,686,292: US and US 6,207,152.

[0017] Several of the monoclonal antibodies referenced above are commercially available from Upstate Biotechnology Incorporated, Lake Placid, N.Y. Monoclonal antibodies DO-24 and DL-21, specific for the extracellular epitope of c-Met, are available from Upstate Biotechnology Incorporated. Monoclonal antibody DQ-13, specific for the intracellular epitope of c- Met, is also available from Upstate Biotechnology Incorporated.

[0018] Various biological activities have been described for HGF and its receptor [see, generally, Chan et al., *Hepatocyte Growth Factor - Scatter Factor* (HGF - *SF) and the C - Met Receptor,* Goldberg and Rosen, eds., Birkhauser Verlag-Basel (1993), pp. 67-79]. It has been observed that levels of HGF increase in the plasma of patients with hepatic failure [Gohda et al., *supra*] and in the plasma [Lindroos et al., *Hepatol.*

13:734-750 (1991)] or serum [Asami et al., *J. Biochem.* 109:8-13 (1991)] of animals with experimentally induced liver damage. The kinetics of this response are usually rapid, and precedes the first round of DNA synthesis during liver regeneration. HGF has also been shown to be a mitogen for certain cell types, including melanocytes, renal tubular cells, keratinocytes, certain endothelial cells and cells of epithelial origin [Matsumoto et al., *Biochem. Biophys. Res. Commun.* 176:45-51 (1991); Igawa et al., *Biochem. Biophys. Res. Commun.* 174:831-838 (1991); Han et al., *Biochem .*, 30:9768-9780 (1991); Rubin et al., *Proc. Natl. Acad. Sci. USA* , 88:415-419 (1991)]. Both HGF and the c-Met protooncogene have been postulated to play a role in microglial reactions to CNS injuries [DiRenzo et al., *Oncogene,* 8:219-222 (1993)].

[0019] HGF can also act as a "scatter factor", an activity that promotes the dissociation and motility of epithelial and vascular endothelial cells in vitro [Stoker et al., *Nature,* 327:239-242 (1987); Weidner et al., *J. Cell Biol.*, 111:2097-2108 (1990); Naldini et al., *EMBO J.*, 10:2867-2878 (1991); Giordano et al., *Proc. Natl. Acad. Sci. USA,* 90:649-653 (1993)]. Moreover, HGF has recently been described as an epithelial morphogen [Montesano et al., *Cell,* 67:901-908 (1991)]. Therefore, HGF has been postulated to be important in tumor invasion [Comoglio, *Hepatocyte Growth Factor - Scatter Factor* (HGF - *SF) and the C - Met Receptor,* Goldberg and Rosen, eds., Birkhauser Verlag-Basel (1993), pp. 131-165]. Bellusci et al., *Oncogene,* 9:1091-1099 (1994) report that HGF can promote motility and invasive properties of NBT-II bladder carcinoma cells.

[0020] c-Met RNA has been detected in several murine myeloid progenitor tumor cell lines [Iyer et al., *Cell Growth and Differentiation,* 1:87- 95 (1990)]. Further, c-Met is expressed in various human solid tumors [Prat et al., *Int. J. Cancer, supra*]. Overexpression of the c-Met oncogene has also been suggested to play a role in the pathogenesis and progression of thyroid tumors derived from follicular epithelium [DiRenzo et al., *Oncogene,* 7:2549-2553 (1992)]. Chronic c-Met/HGF receptor activation has also been observed in certain malignancies [Cooper et al., *EMBO J.*, 5:2623 (1986); Giordano et al., *Nature,* 339:155 (1989)].

[0021] In view of the role of HGF and/or c-Met in potentiating or promoting such diseases or pathological conditions, it would be useful to have a means of substantially reducing or inhibiting one or more of the biological effects elicited by binding of HGF to c-Met.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] Figures 1a-g show alignments of the amino acid sequences of the light and heavy regions of PGIA-01-08, PGIA-03-A9, PGIA-03-A11, PGIA-03-B2, PGIA-04-A5, PGIA-04-A8, and PGIA-05-A1 c-Met scFv antibodies to the germline sequence. C-met scFv alignments to germline. Differences between query sequence and the first germline sequence are bolded and underlined. CDR sequences are highlighted in gray boxes.

[0023] Figure 2 shows inhibition of HGF binding to recombinant c-Met protein by c-Met IgG antibodies 11978, 11994, 12075, and 12119.

[0024] Figure 3 shows inhibition of HGF-dependent cellular proliferation in 184B5 cells by c-Met IgG antibodies 11978, 11994, and 12075.

[0025] Figure 4 shows enhanced tyrosine phosphorylation of the c-Met kinase domain in HCT-116 human colon carcinoma cells following treatment with c-Met IgG antibodies 11978, 11994, 12075, 12119, 12123, 12133, and 12136 determined by Western blot and ELISA.

[0026] Figure 5 shows blocking of HGF binding to c-Met by Fab fragments derived from c-Met antibodies 11978, 11994, 12075, and 12123.

[0027] Figure 6 shows enhanced tyrosine phosphorylation of the c-Met kinase domain by Fab fragments derived from c-Met antibodies 11978, 11994, 12075, 12119, 12123, 12133, and 12136.

[0028] Figure 7 shows inhibition of HGF dependent cellular proliferation of 184B5 cells by Fab fragment derived from c-Met antibody 11994.

[0029] Figure 8 is a representative graph testing the antagonistic and agonistic potential of c-Met IgG antibody11978 in a scatter assay.

[0030] Figure 9 is a graph created from the determination of the wound areas from a H441 cell wound healing (scratch) assay. c-Met IgG antibodies 12133, 12136, 11994, and 12119 show a dose dependent inhibition of cell migration into the scratch.

SUMMARY OF THE INVENTION

[0031] The present invention provides an isolated antibody or antigen-binding portion thereof that binds c-Met, preferably one that binds to primate and human c-Met, and more preferably one that is a human antibody. The invention provides c-Met antibodies that inhibit the binding of HGF to c-Met, and also provides c-Met antibodies that activate c-Met tyrosine phosphorylation.

[0032] The invention provides a pharmaceutical composition comprising the antibody and a pharmaceutically acceptable carrier. The pharmaceutical composition may further comprise another component, such as an anti-tumor agent or an imaging reagent.

[0033] Diagnostic and therapeutic methods are also provided by the invention. Diagnostic methods include a method for diagnosing the presence or location of a c-Met-expressing tissue using a c-Met antibody. A therapeutic method comprises administering the antibody to a subject in need thereof, preferably in conjunction with administration of another therapeutic agent.

[0034] The invention provides an isolated cell line, such as a hybridoma, that produces a c-Met antibody.

[0035] The invention also provides nucleic acid molecules encoding the heavy and/or light chain or antigen-binding portions thereof of a c-Met antibody.

[0036] The invention provides vectors and host cells comprising the nucleic acid molecules, as well as methods of recombinantly producing the polypeptides encoded by the nucleic acid molecules.

[0037] Non-human transgenic animals that express the heavy and/or light chain or antigen-binding portions thereof of a c-Met antibody are also provided. The invention also provides a method for treating a subject in need thereof with an effective amount of a nucleic acid molecule encoding the heavy and/or light chain or antigen-binding portions thereof of a c-Met antibody.

DETAILED DESCRIPTION OF THE INVENTION

Definitions and General Techniques

[0038] Unless otherwise defined herein, scientific and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Generally, nomenclatures used in connection with, and techniques of, cell and tissue culture, molecular biology, immunology, microbiology, genetics and protein and nucleic acid chemistry and hybridization described herein are those well known and commonly used in the art. The methods and techniques of the present invention are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification unless otherwise indicated. See, e.g., Sambrook et al. *Molecular Cloning: A Laboratory Manual*, 2d ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989) and Ausubel et al., *Current Protocols in Molecular Biology*, Greene Publishing Associates (1992), and Harlow and Lane *Using Antibodies: A Laboratory Manual* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1999), which are incorporated herein by reference.

[0039] Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein. The nomenclatures used in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

[0040] The following terms, unless otherwise indicated, shall be understood to have the following meanings:

[0041] As used herein, the terms "hepatocyte growth factor" and "HGF" refer to a growth factor typically having a structure with six domains (finger, Kringle 1, Kringle 2, Kringle 3, Kringle 4 and serine protease domains). Fragments of HGF constitute

HGF with fewer domains and variants of HGF may have some of the domains of HGF repeated; both are included if they still retain their respective ability to bind a HGF receptor. The terms "hepatocyte growth factor" and "HGF" include hepatocyte growth factor from humans and any non-human mammalian species, and in particular rat HGF. The terms as used herein include mature, pre, pre-pro, and pro forms, purified from a natural source, chemically synthesized or recombinantly produced. Human HGF is encoded by the cDNA sequence published by Miyazawa et al., 1989, *supra*, or Nakamura et al., 1989, *supra*. The sequences reported by Miyazawa et al. and Nakamura et al. differ in 14 amino acids. The reason for the differences is not entirely clear; polymorphism or cloning artifacts are among the possibilities. Both sequences are specifically encompassed by the foregoing terms. It will be understood that natural allelic variations exist and can occur among individuals, as demonstrated by one or more amino acid differences in the amino acid sequence of each individual. The terms "hepatocyte growth factor" and "HGF" specifically include the delta5 huHGF as disclosed by Seki et al., *supra*.

[0042] The terms "HGF receptor" and "c-Met" when used herein refer to a cellular receptor for HGF, which typically includes an extracellular domain, a transmembrane domain and an intracellular domain, as well as variants and fragments thereof which retain the ability to bind HGF. The terms "HGF receptor" and "c-Met" include the polypeptide molecule that comprises the full-length, native amino acid sequence encoded by the gene variously known as p190 $^{MET.}$ The present definition specifically encompasses soluble forms of c-Met, and c-Met from natural sources, synthetically produced in vitro or obtained by genetic manipulation including methods of recombinant DNA technology. The c-Met variants or fragments preferably share at least about 65% sequence homology, and more preferably at least about 75% sequence homology with any domain of the human c-Met amino acid sequence published in Rodrigues et al., *Mol. Cell. Biol.*, 11:2962-2970 (1991); Park et al., *Proc. Natl. Acad. Sci.*, 84:6379-6383 (1987); or Ponzetto et al., *Oncogene,* 6:553-559 (1991).

[0043] The term "HGF biological activity" when used herein refers to any mitogenic, motogenic, or morphogenic activities of HGF or any activities occurring as a result of HGF binding to c-Met. The term "c-Met activation" refers to c-Met dimerization or HGF-induced tyrosine kinase activity within c-Met. Activation of c-

Met may occur as a result of HGF binding to c-Met, but may alternatively occur independent of any HGF binding to c-Met. In addition "c-Met activation" may occur following the binding of a c-Met monoclonal antibody to c-Met. HGF biological activity may, for example, be determined in an *in vitro* or *in vivo* assay of HGF-induced cell proliferation, cell scattering, or cell migration. The effect of a HGF receptor antagonist can be determined in an assay suitable for testing the ability of HGF to induce DNA synthesis in cells expressing c-Met such as mink lung cells or human mammary epithelial cells (described in Example 5). DNA synthesis can, for example, be assayed by measuring incorporation of ^{3}H-thymidine into DNA. The effectiveness of the c-Met antagonist can be determined by its ability to block proliferation and incorporation of the ^{3}H-thymidine into DNA. The effect of c-Met antagonists can also be tested *in vivo* in animal models.

[0044] The term "polypeptide" encompasses native or artificial proteins, protein fragments, and polypeptide analogs of a protein sequence. A polypeptide may be monomeric or polymeric.

[0045] The term "isolated protein" or "isolated polypeptide" is a protein or polypeptide that by virtue of its origin or source of derivation, (1) is not associated with naturally associated components that accompany it in its native state, (2) is free of other proteins from the same species, (3) is expressed by a cell from a different species, or (4) does not occur in nature. Thus, a polypeptide that is chemically synthesized or synthesized in a cellular system different from the cell from which it naturally originates will be "isolated" from its naturally associated components. A protein may also be rendered substantially free of naturally associated components by isolation, using protein separation and purification techniques well known in the art.

[0046] A protein or polypeptide is "substantially pure," "substantially homogeneous" or "substantially purified" when at least about 60 to 75% of a sample exhibits a single species of polypeptide. The polypeptide or protein may be monomeric or multimeric. A substantially pure polypeptide or protein will typically comprise about 50%, 60, 70%, 80% or 90% W/W of a protein sample, more usually about 95%, and preferably will be over 99% pure. Protein purity or homogeneity may be indicated by a number of means well known in the art, such as polyacrylamide gel electrophoresis of a protein sample, followed by visualizing a single polypeptide band upon staining the gel with a stain well known in the art. For certain purposes, higher

resolution may be provided by using HPLC or other means well known in the art for purification.

[0047] The term "polypeptide fragment" as used herein refers to a polypeptide that has an amino-terminal and/or carboxy-terminal deletion, but where the remaining amino acid sequence is identical to the corresponding positions in the naturally occurring sequence. Fragments typically are at least 5, 6, 8, or amino acids long, preferably at least 14 amino acids long, more preferably at least amino acids long, usually at least 20 amino acids long, even more preferably at least 70, 80, 90, 100, 150 or 200 amino acids long.

[0048] The term "polypeptide analog" as used herein refers to a polypeptide that is comprised of a segment of at least amino acids that has substantial identity to a portion of an amino acid sequence and that has at least one of the following properties: (1) specific binding to c-Met under suitable binding conditions, (2) ability to block HGF binding to c-Met, or (3) ability to reduce c-Met cell surface expression or tyrosine phosphorylation *in vitro* or *in vivo*. Typically, polypeptide analogs comprise a conservative amino acid substitution (or insertion or deletion) with respect to the naturally occurring sequence. Analogs typically are at least 20 amino acids long, preferably at least 50, 60, 70, 80, 90, 100, 150 or 200 amino acids long or longer, and can often be as long as a full-length naturally occurring polypeptide.

[0049] Preferred amino acid substitutions are those which, (1) reduce susceptibility to proteolysis, (2) reduce susceptibility to oxidation, (3) alter binding affinity for forming protein complexes, (4) alter binding affinities, and (5) confer or modify other physicochemical or functional properties of such analogs. Analogs can include various muteins of a sequence other than the naturally occurring peptide sequence. For example, single or multiple amino acid substitutions (preferably conservative amino acid substitutions) may be made in the naturally occurring sequence (preferably in the portion of the polypeptide outside the domain(s) forming intermolecular contacts. A conservative amino acid substitution should not substantially change the structural characteristics of the parent sequence (e.g., a replacement amino acid should not tend to break a helix that occurs in the parent sequence, or disrupt other types of secondary structure that characterizes the parent sequence). Examples of art-recognized polypeptide secondary and tertiary structures are described in *Proteins, Structures and Molecular Principles* (Creighton, Ed., W. H.

Freeman and Company, New York (1984)); *Introduction to Protein Structure* (C. Branden and J. Tooze, eds., Garland Publishing, New York, N.Y. (1991)); and Thornton et al. *Nature* 354:105 (1991), which are each incorporated herein by reference. Non-peptide analogs are commonly used in the pharmaceutical industry as drugs with properties analogous to those of the template peptide. These types of non-peptide compound are termed "peptide mimetics" or "peptidomimetics". Fauchere, J. *Adv. Drug Res.* 15:29 (1986); Veber and Freidinger *TINS* p.392 (1985); and Evans et al. *J. Med. Chem.* 30:1229 (1987), which are incorporated herein by reference. Such compounds are often developed with the aid of computerized molecular modeling. Peptide mimetics that are structurally similar to therapeutically useful peptides may be used to produce an equivalent therapeutic or prophylactic effect. Generally, peptidomimetics are structurally similar to a paradigm polypeptide (i.e., a polypeptide that has a desired biochemical property or pharmacological activity), such as a human antibody, but have one or more peptide linkages optionally replaced by a linkage selected from the group consisting of: --CH_2NH--, --CH_2S--, -CH_2-CH_2--, --CH=CH-- (cis and trans), --$COCH_2$--, --$CH(OH)CH_2$--, and-CH_2SO-, by methods well known in the art. Systematic substitution of one or more amino acids of a consensus sequence with a D-amino acid of the same type (e.g., D-lysine in place of L-lysine) may also be used to generate more stable peptides. In addition, constrained peptides comprising a consensus sequence or a substantially identical consensus sequence variation may be generated by methods known in the art (Rizo and Gierasch *Ann. Rev. Biochem.* 61:387 (1992), incorporated herein by reference); for example, by adding internal cysteine residues capable of forming intramolecular disulfide bridges which cyclize the peptide.

[0050] An "immunoglobulin" is a tetrameric molecule. In a naturally occurring immunoglobulin, each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to l or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function. Human light chains are classified as either kappa or lambda chains. Heavy chains are classified as μ, Δ, γ, α, or ε, and define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. Within light and heavy chains, the

variable and constant regions are joined by a "J" region of about 12 or more amino acids, with the heavy chain also including a "D" region of about 10 more amino acids. See generally, *Fundamental Immunology* Ch. 7 (Paul, W., ea., 2nd ed. Raven Press, N.Y. (1989)) (incorporated by reference in its entirety for all purposes). The variable regions of each light/heavy chain pair form the antibody binding site such that an intact immunoglobulin has two binding sites.

[0051] Immunoglobulin chains exhibit the same general structure of relatively conserved framework regions (FR) joined by three hypervariable regions, also called complementarily determining regions or CDRs. The CDRs from the two chains of each pair are aligned by the framework regions, enabling binding to a specific epitope. From N-terminus to C-terminus, both light and heavy chains comprise the domains FRI, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The assignment of amino acids to each domain is in accordance with the definitions of Kabat, et al., *Sequences of Proteins of Immunological Interest* (National Institutes of Health, Bethesda, Md. (1987 and 1991)), or Chothia & Lesk *J. Mol. Biol.* 196:901-917 (1987); Chothia et al. *Nature* 342:878-883 (1989).

[0052] An "antibody" refers to an intact immunoglobulin or to an antigen-binding portion thereof that competes with the intact antibody for specific binding. Antigen-binding portions may be produced by recombinant DNA techniques or by enzymatic or chemical cleavage of intact antibodies. Antigen-binding portions include, *inter alia*, Fab, Fab', $F(ab')_2$, Fv, dAb, and complementarily determining region (CDR) fragments, single-chain antibodies (scFv), chimeric antibodies, diabodies and polypeptides that contain at least a portion of an immunoglobulin that is sufficient to confer specific antigen binding to the polypeptide.

[0053] An Fab fragment is a monovalent fragment consisting of the VL, VH, CL and CH1 domains; a F(ab')2 fragment is a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consists of the VH and CH1 domains; an Fv fragment consists of the VL and VH domains of a single arm of an antibody; and a dAb fragment (Ward et al., *Nature* 341:544-546, 1989) consists of a VH domain.

[0054] A single-chain antibody (scFv) is an antibody in which a VL and VH regions are paired to form a monovalent molecule via a synthetic linker that enables them to be made as a single protein chain (Bird et al., *Science* 242:423-426, 1988 and

Huston et al., *Proc. Natl. Acad. Sci.* USA 85:5879-5883, 1988). Diabodies are bivalent, bispecific antibodies in which VH and VL domains are expressed on a single polypeptide chain, but using a linker that is too short to allow for pairing between the two domains on the same chain, thereby forcing the domains to pair with complementary domains of another chain and creating two antigen binding sites (see e.g., Holliger, P., et al., *Proc. Natl. Acad. Sci. USA* 90:64446448, 1993, and Poljak, R. J., et al., *Structure* 2:1121 - 1123, 1994). One or more CDRs may be incorporated into a molecule either covalently or noncovalently to make it an immunoadhesin. An immunoadhesin may incorporate the CDR(s) as part of a larger polypeptide chain, may covalently link the CDR(s) to another polypeptide chain, or may incorporate the CDR(s) noncovalently. The CDRs permit the immunoadhesin to specifically bind to a particular antigen of interest.

[0055] An antibody may have one or more binding sites. If there is more than one binding site, the binding sites may be identical to one another or may be different. For instance, a naturally occurring immunoglobulin has two identical binding sites; a single-chain antibody or Fab fragment has one binding site, while a "bispecific" or "bifunctional" antibody has two different binding sites.

[0056] An "isolated antibody" is an antibody that (1) is not associated with naturally-associated components, including other naturally-associated antibodies, that accompany it in its native state, (2) is free of other proteins from the same species, (3) is expressed by a cell from a different species, or (4) does not occur in nature.

[0057] Examples of isolated antibodies include an c-Met antibody that has been affinity purified using c-Met is an antigen, an anti- c-Met antibody that has been synthesized by a hybridoma or other cell line *in vitro*, and a human c-Met antibody derived from a transgenic mouse.

[0058] The term "human antibody" includes all antibodies that have one or more variable and constant regions derived from human immunoglobulin sequences.

[0059] In a preferred embodiment, all of the variable and constant domains are derived from human immunoglobulin sequences (a fully human antibody). These antibodies may be prepared in a variety of ways, as described below.

[0060] A "humanized antibody" is an antibody that is derived from a non-human species, in which certain amino acids in the framework and constant domains of the heavy and light chains have been mutated so as to avoid or abrogate an immune

response in humans. Alternatively, a humanized antibody may be produced by fusing the constant domains from a human antibody to the variable domains of a non-human species. Examples of how to make humanized antibodies may be found in United States Patent Nos. 6, 054,297, 5,886,152, and 5,877,293.

[0061] The term "chimeric antibody" refers to an antibody that contains one or more regions from one antibody and one or more regions from one or more other antibodies. In a preferred embodiment, one or more of the CDRs are derived from a human c-Met antibody. In a more preferred embodiment, all of the CDRs are derived from a human c-Met antibody. In another preferred embodiment, the CDRs from more than one human c-Met antibody are mixed and matched in a chimeric antibody. For instance, a chimeric antibody may comprise a CDR1 from the light chain of a first human c-Met antibody may be combined with CDR2 and CDR3 from the light chain of a second human c-Met antibody, and the CDRs from the heavy chain may be derived from a third c-Met antibody. Further, the framework regions may be derived from one of the same c-Met antibodies, from one or more different antibodies, such as a human antibody, or from a humanized antibody. A "neutralizing antibody" or "an inhibitory antibody" is an antibody that inhibits the binding of c-Met to HGF when an excess of the c-Met antibody reduces the amount of HGF bound to c-Met by at least about 20%. In a preferred embodiment, the antibody reduces the amount of HGF bound to c-Met by at least 40%, more preferably 60%, even more preferably 80%, or even more preferably 85%. The binding reduction may be measured by any means known to one of ordinary skill in the art, for example, as measured in an *in vitro* competitive binding assay. An example of measuring the reduction in binding of HGF to c-Met is presented below in Example 4.

[0062] An "activating antibody" is an antibody that activates c-Met by at least about 20% when added to a cell, tissue, or organism expressing c-Met, when compared to the activation achieved by an equivalent molar amount of HGF. In a preferred embodiment, the antibody activates c-Met activity by at least 40%, more preferably 60%, even more preferably 80%, or even more preferably 85% of the level of activation achieved by an equivalent molar amount of HGF. In a more preferred embodiment, the activating antibody is added in the presence of HGF. In another preferred embodiment, the activity of the activating antibody is measured by determining the amount of tyrosine phosphorylation and activation of c-Met.

[0063] Fragments or analogs of antibodies can be readily prepared by those of ordinary skill in the art following the teachings of this specification. Preferred amino and carboxy-termini of fragments or analogs occur near boundaries of functional domains. Structural and functional domains can be identified by comparison of the nucleotide and/or amino acid sequence data to public or proprietary sequence databases. Preferably, computerized comparison methods are used to identify sequence motifs or predicted protein conformation domains that occur in other proteins of known structure and/or function. Methods to identify protein sequences that fold into a known three-dimensional structure have been described by Bowie et al. *Science* 253:164(1991).

[0064] The term "surface plasmon resonance", as used herein, refers to an optical phenomenon that allows for the analysis of real-time biospecific interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIAcore system (Pharmacia Biosensor AB, Uppsala, Sweden and Piscataway, N.J.). For further descriptions, see Jonsson, U., et al. (1993) *Ann. Biol. Clin.* 51:19-26; Jonsson, U., et al. (1991) *Biotechniques* 11:620-627; Johnsson, B., et al. (1995) *J. Mol. Recognit.* 8:125-131; and Johnsson, B., et al. (1991) *Anal. Biochem.* 198:268-277.

[0065] The term "K_{off}" refers to the off rate constant for dissociation of an antibody from the antibody/antigen complex.

[0066] The term "K_d" refers to the dissociation constant of a particular antibody-antigen interaction.

[0067] The term "epitope" includes any molecular determinant capable of specific binding to an immunoglobulin or T-cell receptor. Epitopes usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three-dimensional structural characteristics, as well as specific charge characteristics. An antibody is said to specifically bind an antigen when the dissociation constant is <1 M, preferably <100 nM, preferably <10 nM, and most preferably <1 nM.

[0068] As used herein, the twenty conventional amino acids and their abbreviations follow conventional usage. See *Immunology - A Synthesis* (2nd Edition, E.S. Golub and D.R. Gren, Eds., Sinauer Associates, Sunderland, Mass.(1991)), which is incorporated herein by reference. Stereoisomers (e.g., D-amino acids) of the

twenty conventional amino acids, unnatural amino acids such as α-, α-2,5 disubstituted amino acids, N-alkyl amino acids, lactic acid, and other unconventional amino acids may also be suitable components for polypeptides of the present invention. Examples of unconventional amino acids include: 4-hydroxyproline, γ-carboxyglutamate, ε-N,N,N-trimethyllysine, ε-N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, s-N-methyl arginine, and other similar amino acids and imino acids (e.g., 4-hydroxyproline). In the polypeptide notation used herein, the left-hand direction is the amino terminal direction and the right-hand direction is the carboxy-terminal direction, in accordance with standard usage and convention.

[0069] The term "polynucleotide" as referred to herein means a polymeric form of nucleotides of at least 10 bases in length, either ribonucleotides or deoxynucleotides or a modified form of either type of nucleotide. The term includes single and double stranded forms of DNA.

[0070] The term "isolated polynucleotide" as used herein shall mean a polynucleotide of genomic, cDNA, or synthetic origin or some combination thereof, which by virtue of its origin the "isolated polynucleotide", (1) is not associated with all or a portion of a polynucleotide in which the "isolated polynucleotide" is found in nature, (2) is operably linked to a polynucleotide which it is not linked to in nature, or (3) does not occur in nature as part of a larger sequence.

[0071] The term "oligonucleotides" referred to herein includes naturally occurring, and modified nucleotides linked together by naturally occurring, and non-naturally occurring oligonucleotide linkages. Oligonucleotides are a polynucleotide subset generally comprising a length of 200 bases or fewer. Preferably oligonucleotides are 10 to 60 bases in length and most preferably 12, 13, 14, 15, 16, 17, 18, 19, or to 40 bases in length. Oligonucleotides are usually single stranded, e.g. for probes; although oligonucleotides may be double stranded, e.g. for use in the construction of a gene mutant. Oligonucleotides of the invention can be either sense or antisense oligonucleotides.

[0072] The term "naturally occurring nucleotides" referred to herein includes deoxyribonucleotides and ribonucleotides. The term "modified nucleotides" referred to herein includes nucleotides with modified or substituted sugar groups and the like.

[0073] The term "oligonucleotide linkages" referred to herein includes Oligonucleotides linkages such as phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phoshoraniladate, phosphoroamidate, and the like. See e.g., LaPlanche et al. *Nucl. Acids Res.* 14:9081 (1986); Stec et al. *J. Am. Chem. Soc.* 106:6077 (1984); Stein et al. *Nucl. Acids Res.* 16:3209 (1988); Zon et al. *Anti-Cancer Drug Design* 6:539 (1991); Zon et al. *Oligonucleotides and Analogues: A Practical Approach*, pp. 87-108 (F. Eckstein, Ed., Oxford University Press, Oxford England (1991)); Stec et al. U.S. Patent No. 5,151,510; Uhlmann and Peyman *Chemical Reviews* 90:543 (1990), the disclosures of which are hereby incorporated by reference. An oligonucleotide can include a label for detection, if desired.

[0074] "Operably linked" sequences include both expression control sequences that are contiguous with the gene of interest and expression control sequences that act in trans or at a distance to control the gene of interest. The term "expression control sequence" as used herein refers to polynucleotide sequences that are necessary to effect the expression and processing of coding sequences to which they are ligated. Expression control sequences include appropriate transcription initiation, termination, promoter and enhancer sequences; efficient RNA processing signals such as splicing and polyadenylation signals; sequences that stabilize cytoplasmic mRNA; sequences that enhance translation efficiency (i.e., Kozak consensus sequence); sequences that enhance protein stability; and when desired, sequences that enhance protein secretion. The nature of such control sequences differs depending upon the host organism; in prokaryotes, such control sequences generally include promoter, ribosomal binding site, and transcription termination sequence; in eukaryotes, generally, such control sequences include promoters and transcription termination sequence. The term "control sequences" is intended to include, at a minimum, all components whose presence is essential for expression and processing, and can also include additional components whose presence is advantageous, for example, leader sequences, and fusion partner sequences. The term "vector", as used herein, is intended to refer to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments may be ligated. Another

type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome.

[0075] Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked.

[0076] Such vectors are referred to herein as "recombinant expression vectors" (or simply, "expression vectors"). In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" may be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (e. g., replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

[0077] The term "recombinant host cell" (or simply "host cell"), as used herein, is intended to refer to a cell into which a recombinant expression vector has been introduced. It should be understood that such terms are intended to refer not only to the particular subject cell but also to the progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term "host cell" as used herein.

[0078] The term "selectively hybridize" referred to herein means to detectably and specifically bind. Polynucleotides, oligonucleotides, and fragments thereof in accordance with the invention selectively hybridize to nucleic acid strands under hybridization and wash conditions that minimize appreciable amounts of detectable binding to nonspecific nucleic acids. "High stringency" or "highly stringent" conditions can be used to achieve selective hybridization conditions as known in the art and discussed herein. An example of "high stringency" or "highly stringent" conditions is a method of incubating a polynucleotide with another polynucleotide, wherein one polynucleotide may be affixed to a solid surface such as a membrane, in

a hybridization buffer of 6X SSPE or SSC, 50% formamide, SX Denhardt's reagent, 0.5% SDS, 100 μg/ml denatured, fragmented salmon sperm DNA at a hybridization temperature of 42°C for 12-16 hours, followed by twice washing at 55°C using a wash buffer of 1X SSC, 0.5% SDS. See also Sambrook et al., *supra*, pp. 9.50-9.55.

[0079] The term "percent sequence identity" in the context of nucleic acid sequences refers to the residues in two sequences that are the same when aligned for maximum correspondence. The length of sequence identity comparison may be over a stretch of at least about nine nucleotides, usually at least about 18 nucleotides, more usually at least about 24 nucleotides, typically at least about 28 nucleotides, more typically at least about 32 nucleotides, and preferably at least about 36, 48 or more nucleotides. There are a number of different algorithms known in the art that can be used to measure nucleotide sequence identity. For instance, polynucleotide sequences can be compared using FASTA, Gap, or Bestfit, which are programs in Wisconsin Package Version 10.0, Genetics Computer Group (GCG), Madison, Wisconsin. FASTA, which includes, e.g., the programs FASTA2 and FASTA3, provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson, *Methods Enzymol.* 183: 63-98 (1990); Pearson, *Methods Mol. Biol.* 132: 185-219 (2000); Pearson, *Methods Enzymol.* 266: 227-258 (1996); Pearson, *J. Mol. Biol.* 276: 71-84 (1998; herein incorporated by reference). Unless otherwise specified, default parameters for a particular program or algorithm are used. For instance, percent sequence identity between nucleic acid sequences can be determined using FASTA with its default parameters (a word size of 6 and the NOPAM factor for the scoring matrix) or using Gap with its default parameters as provided in GCG Version 6.1, herein incorporated by reference.

[0080] A reference to a nucleic acid sequence encompasses its complement unless otherwise specified. Thus, a reference to a nucleic acid molecule having a particular sequence should be understood to encompass its complementary strand, with its complementary sequence.

[0081] In the molecular biology art, researchers use the terms "percent sequence identity", "percent sequence similarity" and "percent sequence homology" interchangeably. In this application, these terms shall have the same meaning with respect to nucleic acid sequences only.

[0082] The term "substantial similarity" or "substantial sequence similarity," when referring to a nucleic acid or fragment thereof, indicates that, when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 85%, preferably at least about 90%, and more preferably at least about 95%, 96%, 97%, 98% or 99% of the nucleotide bases, as measured by any well-known algorithm of sequence identity, such as FASTA, BLAST or Gap, as discussed above.

[0083] As applied to polypeptides, the term "substantial identity" means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 75% or 80% sequence identity, preferably at least 90% or 95% sequence identity, even more preferably at least 98% or 99% sequence identity. Preferably, residue positions that are not identical differ by conservative amino acid substitutions. A "conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (e. g., charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein. In cases where two or more amino acid sequences differ from each other by conservative substitutions, the percent sequence identity or degree of similarity may be adjusted upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well known to those of skill in the art. See, e.g., Pearson, *Methods Mol. Biol.* 24: 307-31 (1994), herein incorporated by reference. Examples of groups of amino acids that have side chains with similar chemical properties include 1) aliphatic side chains: glycine, alanine, valine, leucine and isoleucine; 2) aliphatic-hydroxyl side chains: serine and threonine; 3) amide-containing side chains: asparagine and glutamine; 4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; 5) basic side chains: lysine, arginine, and histidine; and 6) sulfur-containing side chains are cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, glutamate-aspartate, and asparagine-glutamine.

[0084] Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet et al., *Science* 256: 1443-45 (1992), herein incorporated by reference. A "moderately conservative"

replacement is any change having a nonnegative value in the PAM250 log-likelihood matrix.

[0085] Sequence similarity for polypeptides, which is also referred to as sequence identity, is typically measured using sequence analysis software. Protein analysis software matches similar sequences using measures of similarity assigned to various substitutions, deletions, and other modifications, including conservative amino acid substitutions. For instance, GCG contains programs such as "Gap" and "Bestfit" which can be used with default parameters to determine sequence homology or sequence identity between closely related polypeptides, such as homologous.

[0086] Polypeptides from different species of organisms or between a wild type protein and a mutein thereof. See, e.g., GCG Version 6.1. Polypeptide sequences also can be compared using FASTA using default or recommended parameters, a program in GCG Version 6.1. FASTA (e.g., FASTA2 and FASTA3) provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson (1990); Pearson (2000). Another preferred algorithm when comparing a sequence of the invention to a database containing a large number of sequences from different organisms is the computer program BLAST, especially blastp or tblastn, using default parameters. See, e.g., Altschul et al., *J. Mol. Biol.* 215: 403410 (1990); Altschul et al., *Nucleic Acids* Res. 25:3389-402 (1997); herein incorporated by reference.

[0087] The length of polypeptide sequences compared for homology will generally be at least about 16 amino acid residues, usually at least about residues, more usually at least about 24 residues, typically at least about 28 residues, and preferably more than about 35 residues. When searching a database containing sequences from a large number of different organisms, it is preferable to compare amino acid sequences.

[0088] As used herein, the terms "label" or "labeled" refers to incorporation of another molecule in the antibody. In one embodiment, the label is a detectable marker, e.g., incorporation of a radiolabeled amino acid or attachment to a polypeptide of biotinyl moieties that can be detected by marked avidin (e.g., streptavidin containing a fluorescent marker or enzymatic activity that can be detected by optical or calorimetric methods). In another embodiment, the label or marker can be therapeutic, e.g., a drug conjugate or toxin. Various methods of labeling polypeptides and

glycoproteins are known in the art and may be used. Examples of labels for polypeptides include, but are not limited to, the following: radioisotopes or radionuclides (e.g., ^{3}H, ^{14}C, ^{15}N, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I), fluorescent labels (e.g., FITC, rhodamine, lanthanide phosphors), enzymatic labels (e.g., horseradish peroxidase, β-galactosidase, luciferase, alkaline phosphatase), chemiluminescent markers, biotinyl groups, predetermined polypeptide epitopes recognized by a secondary reporter (e.g., leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags), magnetic agents, such as gadolinium chelates, toxins such as pertussis toxin, taxol, cytochalasin B. gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof.

[0089] In some embodiments, labels are attached by spacer arms of various lengths to reduce potential steric hindrance.

[0090] The term "agent" is used herein to denote a chemical compound, a mixture of chemical compounds, a biological macromolecule, or an extract made from biological materials. The term "pharmaceutical agent or drug" as used herein refers to a chemical compound or composition capable of inducing a desired therapeutic effect when properly administered to a patient. Other chemistry terms herein are used according to conventional usage in the art, as exemplified by The McGraw-Hill *Dictionary of Chemical Terms* (Parker, S., Ed., McGraw-Hill, San Francisco (1985)), incorporated herein by reference).

[0091] The term "antineoplastic agent" is used herein to refer to agents that have the functional property of inhibiting a development or progression of a neoplasm in a human, particularly a malignant (cancerous) lesion, such as a carcinoma, sarcoma, lymphoma, or leukemia. Inhibition of metastasis is frequently a property of antineoplastic agents.

[0092] The term "patient" includes human and veterinary subjects.

Human c-Met Antibodies and Characterization Thereof

[0093] Human antibodies avoid certain of the problems associated with antibodies that possess mouse or rat variable and/or constant regions. The presence of such mouse or rat derived sequences can lead to the rapid clearance of the antibodies or can lead to the generation of an immune response against the antibody by a patient.

[0094] Therefore, in one embodiment, the invention provides humanized anti- c-Met antibodies. In a preferred embodiment, the invention provides fully human c-Met antibodies by introducing human immunoglobulin genes into a rodent so that the rodent produces fully human antibodies. More preferred are fully human anti-human c-Met antibodies. Fully human c-Met antibodies directed against human c-Met are expected to minimize the immunogenic and allergic responses intrinsic to mouse or mouse-derivatized monoclonal antibodies (Mabs) and thus to increase the efficacy and safety of the administered antibodies. The use of fully human antibodies can be expected to provide a substantial advantage in the treatment of chronic and recurring human diseases, such as inflammation and cancer, which may require repeated antibody administrations. In another embodiment, the invention provides a c-Met antibody that does not bind complement.

[0095] In a preferred embodiment, the c-Met antibody is selected from PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, and PGIA-05-A1 or a fragment of any one thereof. In a preferred embodiment, the c-Met antibody is selected from PGIA-01-A8, PGIA-03-A9, PGIA-03-A11, PGIA-03-B2, PGIA-04-A5, PGIA-04-A8, and PGIA-05-A1 or a fragment of any one thereof. In a preferred embodiment the c-Met antibody is selected from PGIA-03-A9, PGIA-04-A5, and PGIA-04-A8 or a fragment of any one thereof.

[0096] Table 1 shows the amino acid sequences of the scFvs PGIA-01-A1 through PGIA-05-A1 above.

TABLE 1

PGIA-1-A1

EVQLLESGRGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGS
TYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARWGQGTTVTVSSGGGGS
GGGGSGGGGSAQAVLTQPSSVSGAPGQRVTISCTGSSSNIGADYDVHWYQQLPGTAP
KLLIYGNNNRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYYCQSYDNSPDAYVVF
GGGTKLTVLS SEQ ID NO:1,

PGIA-1-A2

QVQLVQSGAEVRKPGASVKVSCKTSGYTFIDYYIHWVRQAPGQGLEWMGWVNPVTGT
SGSSPNFRGRVTMTTDTSGNTAYMELRSLRSDDTAVFYCARRHQQSLDYWGQGTLVT
VSSGGGGSGGGGSGGGGSAQSVLTQPPSVSAPPGQKVTISCSGSSSNIGTNYVSWYQ
QLPGTAPKLLIYDNHKRPSVIPDRFSGSKSGTSATLGISGLQTGDEADYYCGTWDYS
LSTWVFGGGTKLTVLG SEQ ID NO:2,

PGIA-1-A3

QLQLQESGPGLVKPSGTLSLTCAVSGDSVSSYYWWSWVRQPPGKGLEWIGEIFRDGS
SNYNRSLKSRVTISPDKPKNQFSLRLSSVTAADTAIYYCARHIRGYDAFDIWGRGTL
VTVSSGGGGSGGGGSGGGGSAQSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVH
WYQQFPGRAPKLLIYGNTNRPSGVPDRFSGSKSDISASLAITGLQAEDEADYYCQSY
DSNLTGVFGGGT SEQ ID NO:3,

PGIA-1-A4

QVQLVQSGAEVRKPGASVKVSCKTSGYTFMDYYIHWVRQAPGQGLEWMGWSNPVTGT
SGSSPKFRGRVTLTTDTSGNTAYLDLRSLRSDDTAVFYCARRHQQSLDYWGQGTMVT
VSSGGGGSGGGGSGGGGSAQSVLTQPPSVSAAPGQKVTISCSGSSSNIGNNYVSWYQ
QLPGTAPKLLMYENSKRPSGIPDRFSGSKSGTSGTLGITGLQTGDEADYYCGTWDTS
LRAWVFGGGTKVTVLG SEQ ID NO:4,

PGIA-1-A5

QVQLQQSGAEVRKPGASAKVSCKTSGYTFIDYYIHWVRQAPGQGLEWMGWINPVTGA
SGSSPNFRGRVTLTTDTSGNTAYMELRSLRSDDTAVFYCARRHQQSLDYWGRGTTVT
VSSGGGGSGGGGSGGGGSAQSVVTQPPSVSAAPGQKVTISCSGRTSNIGNNYVSWYQ
QVPGAPPKLLIFDNNKRPSGTPARFSGSKSGTSATLAISGLQTGDEADYYCGTWDTT
LRGFVFGPGTKVTVLG SEQ ID NO:5,

PGIA-1-A6

QLQLQESGPGLVKPSGTLSLTCAVSGGSISSTNWWSWVRQPPGKGLEWIGEIYHSGS
TNYNPSLKSRVTISVDKSKNHFSLNLSSVTAADTAVYYCARDSMGSTGWHYGMDLWG
RGTLVTVSSGGGGSGGGGSGGGGSAQSALTQPPSASGSPGQSVTISCSGSSSDIGDY
NHVSWYQQHPGKAPKLMIYDVNKWPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYY
CSSYSGIYNLVFGGGTKVTVLG SEQ ID NO:6,

PGIA-1-A7

EVQLVQSGAEVKKPGSSVKVSCKASGGTFKTYAINWVRQAPGQGLEWMGGIIPVLGT
ANYVQKFQGRVTITADESTTTAYMELRGLRSEDTAVYYCARGEGSGWYDHYYGLDVW
GQGTLVTVSSGGGGSGGGGSGGGGSAQSVLTQPPSASGTPGQRVTISCSGSSSNIGS
NTVNWYRQLPGTAPKLLIFGDDQRPSGVPDRFSGSRSGTSVSLAISGLQSEDEADYY
CAAWDDSLNGGVFGGGTKLTVLG SEQ ID NO:7,

PGIA-1-A8

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGS
TYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDHYYDSSGYLDYWGQG
TLVTVSSGGGGSGGGGSGGGGSALNFMLTQPHSVSESPGKTVTISCTRSSGSIAFDY
VQWYQQRPGSAPTTVIYEDNQRPSGVPDRFSASIDSSSNSASLTISALKTEDEADYY
CQSYDNSNSWVFGGGTKLTVLG SEQ ID NO:8,

PGIA-1-A9

KVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGS
TYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDDVRNAFDIWGRGTTV
TVSSGGGGSGGGGSGGGGSAQSVLTQPPSVSVSPGQTTSITCSRDKLGEQYVYWYQQ
RPGQSPILLLYQDSRRPSWIPERFSGSNSGDTATLTISGTQALDEADYYCQAWDNSS
YVAFGGGTKVTVLG SEQ ID NO:9,

PGIA-1-A10

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGS
TYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARGGELWNPYLDYWGQGT
LVTVSSGGGGSGGGGSGGGGSALPVLTQPPSVSVAPGKTARITCGGNDIASKSVQWF
QQKPGQAPVLVIYYDSDRPSGIPERFSGSNSENTATLTISRVEAGDEADYYCQVWDS
SSDHPVFGGGTKLTVLG SEQ ID NO:10,

PGIA-1-A11

QVQLVQSGAEVKKPGESLKISCKGSGYTFTNYWIAWVRQMPGKGLEWMGIIYPDDSD
TRYNPSFQGQVTMSADKSIDTAYLQWSSLKASDTAIYYCARPSGWNDNGYFDYWGRG
TTVTVSSGGGGSGGGGSGGGGSALNFMLTQPHSVSASPGKTVTLSCTGSSGSIASNY
VQWYRQRPGSAPTTVIYDDNQRPSGVPDRFSGSIDSSSNSASLTISGLKTEDEADYY
CQSFDNDNHWVFGGGTKLTVLG SEQ ID NO:11,

PGIA-1-A12

QVQLQESGPGLVRSSGILSLTCSVSGVSVSSNNWWSWVRQTPGKGLEWIGEIYQTGT
TNYNPSLKSRVAISLDKSRNQFSLILKSVTAADTAVYYCARTSSAWSNADWGKGTMV

TVSSGGGGSGGGGSGGGGSALSSELTQDPSASGSPGQSVSISCTGTSSDVGGYNYVS
WYQQHPGKAPKLMISEVTKRPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYYCSSF
GANNNYLVFGGGTKLTVLG SEQ ID NO:12,

PGIA-1-B1

QVQLQESGPRLVKPSQTLSLTCTVSNDSIISGDYFWSWIRQPPGKGLEWIGNIFYTG
STSYNPSLKSRLTMSLDTSKNQFSLRLSSVTAADTAVYFCARGRQGMNWNSGTYFDS
WGRGTLVTVSSGGGGSGGGGSGGGGSALSYVLTQPPSVSVAPGKTANITCGGKNIGN
KSVQWYQQKPGQAPVVVMYYDSDRPSGIPERFSGSNAGNTATLTIDRVEAGDEADYY
CQVWDKSSDRPVFGGGTKLTVLG SEQ ID NO:13,

PGIA-1B2

QVQLVQSGAEVKKPGASVKVSCKTSGYTFMEYYIHWVRQAPGQGLEWMGWSNPVTGT
SGSSPKFRGRVTLTTDTSGNTAYLDLRSLRSDDTAVFYCARRHQQSLDYWGQGTLVT
VSSGGGGSGGGGSGGGGSAQSVVTQPPSASGSPGQSVTISCSGYSSSNIGNNAVSWY
QQLPGTAPKLLIFDNNKRPSGIPARFSGSQSGTTATLGITGLQTGDEADYFCGTWDS
SLSAFVFGSGTKVTVLG SEQ ID NO:14,

PGIA-2-A1

EVQLVQSGAEVKKPGSSVKVSCKASGGSFSNYDFSWVRQAPGQGLEWMGEIINAFGS
SRYAQKFQDRVTITADESASTAYMELRGLTSEDTATYYCARAERWELNMAFDMWGRG
TLVTVSSGGGGSGGGGSGGGGSAQSVLTQPPSVSVAPGQTARITCGGDNIGRKNVHW
YQQRPGLAPVLVVYDDTDRPSGIPERFSGSNSGDTATLTITWVEAGDEADYYCQLWD
SDTYDVLFGGGTKLTVLG SEQ ID NO:15,

PGIA-2-A2

EVQLVQSGAEVKKPGSSVKVSCKSSGGPFSSYGISWVRQAPGQGLEWMGGISPIFGT
ANYAQKFQGRVTITADESTETAYMELSSLRSEDTAVYYCARDESPVGFYALDIWGRG
TTVTVSSGGGGSGGGGSGGGGSALSYELTQPPSVSVAPGQTARINCGGDKIGSRSVH
WYQQKPGQAPVMVVYDDSDRPSGIPERFSGSNSGNTATLTISSVEAGDEADYYCQVW
DGSTDPWVFGGGTKVTVLG SEQ ID NO:16,

PGIA-2-A3

EVQLVQSGAEMKKPGSSVKVSCKASGGTFSSYAVNWVRQAPGQGLEWMGGIIPIFDT
SNYAQKFQGRLTMTADDSTNTAYMELRSLRSEDTAVYYCARGAPRGTVMAFSSYYFD
LWGQGTLVTVSSGGGGSGGGGSGGGGSALNFMLTQPHSVSESPGKTVIISCAGSGGN
IATNYVQWYQHRPGSAPITVIYEDNQRPSGVPDRFSGSVDSSSNSASLTISGLQTED
EADYYCHSYDNTDQGVFGTGTKVTVLG SEQ ID NO:17,

PGIA-2-A4

EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYDMHWVRQAPGKGLEWVSSISWSGGT
IGYADSVKGRFTVSRDNAKNSLYLQMNSVRAEDTALYYCAKDRGAVAALPDYQYGMD
VWGRGTLVTVSSGGGGSGGGGSGGGGSAQSALTQPASVSGSPGQSITISCTGTSSDI

GSYNLVSWYQQHPGKAPKLMIYEDYKRASGVSNHFSGSKSGNTASLTISGLQAEDEA
DYYCSSYAGSSAWVFGGGTKVTVLG SEQ ID NO:18,

PGIA-2-A5

EVQLVQSGAEVRKPGSSMKVSCKASGDTFRNFAFSWVRQAPGQGLEWMGGVIPLVGP
PKYAQKFQGRLTITADESTSTSYMDLTSLTLEDTAVYFCARGGVYAPFDKWGQGTLV
TVSSGGGGSGGGGSGGGGSAQSVVTQPPSVSEAPRQRVTISCSGSSSNIGNNAVNWY
QQLPGKAPKLLIYYNDLLPSGVSDRFSGSKSGTSASLAISGLQSEDEADYYCAAWDD
SLNGWVFGGGTKVTVLG SEQ ID NO:19,

PGIA-2-A6

EVQLVQSGAEVKKPGSSVKVSCKASGGTFKTYAINWVRQAPGQGLEWMGGIIPVLGT
ANYVQKFQGRVTITADESTTTAYMELRGLRSEDTAVYYCARGEGSGWYDHYYGLDVW
GQGTLVTVSSGGGGSGGGGSGGGGSAQSVLTQPPSASGTPGQRVTISCSGSSSNIGS
NTVNWYRQLPGTAPKLLIFGDDQRPSGVPDRFSGSRSGTSVSLAISGLQSEDEADYY
CAAWDDSLNGGVFGGGTKLTVLG SEQ ID NO:20,

PGIA-2-A7

QLQLQESGPGLVKPSGTLSLTCAVSGGSISTSDWWSWVRRPPGKGLEWIGEIYHSGS
TNYHPSLKSRVTISLDKSKNQFSLKLSSVTAADTAVYYCAREGGHSGSYPLDYWGKG
TLVTVSSGGGGSGGGGSGGGGSAQAVLTQPSSVSAAPGQKVTISCSGSSSNIGNNYV
SWYQQLPGTAPKLLIYDNNKRPSGIPDRFSGSRSGTSATLGITGLQTGDEADYYCGT
WDSSLSAVVFGTGTKLTVLG SEQ ID NO:21,

PGIA-2-A8

QLQLQESGPGLVKPSGTLSLTCAVSGGSISSTNWWSWVRQPPGKGLEWIGEIYHSGS
TNYNPSLKSRVTISVDKSKNHFSLNLSSVTAADTAVYYCARDSMGSTGWHYGMDLWG
KGTLVTVSSGGGGSGGGGSGGGGSAQSALTQPASVSGSPGQSIAISCTGTSSDVGGY
NYVSWYQQHPGKAPKLMIYAVTNRPSGVSDRFSGSKSGNTASLTISGLQADDEADYY
CSSYTSSSSLVFGGGTKLTVLG SEQ ID NO:22,

PGIA-2-A9

GVQLVESGGGLVKPGGSLRLSCAASGFTFSSYTMNWVRQAPGKGLEWVSYISSSGSA
TYYADSVKGRFTISRDNANNSLYLQMNSLRAEDTAVYYCARGYRYGMDVWGQGTLVT
VSSGGGGSGGGGSGGGGSGIVMTQSPSTLSASVGDRVTITCRASQGISSWLAWYQQK
PGRAPKVLIYKASTLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPW
TFGQGTKLEIKR SEQ ID NO:23,

PGIA-2-A10

EVQLLESGGGLVQPGGSLRLTCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGS
TYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDLAVAGIDYWGRGTMV
TVSSGGGGSGGGGSGGGGSAQSVLTQPPSASGTPGQRVTISCSGSSSNIRSNYVYWY
QQFPGTAPKLLIYRNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDD
TLDAYVFAAGTKLTVLG SEQ ID NO:24,

PGIA-2-A11

QVQLQESGPGLVKPSGTLSLTCAVSGGSISTSDWWSWVRRPPGKGLEWIGEIYHSGS
TNYHPSLKSRVTISLDKSKNQFSLKLSSVTAADTAVYYCAREGGHSGSYPLDYWGQG
TLVTVSSGGGGSGGGGSGGGGSALNFMLTQPHSVSGSPGRTVTISCTRSSGSIATNY
VQWYQQRPGSSPTIVIYEDNQRPSGVPDRFSGSIDTSSNSASLTISGLKTEDEADYY
CQSYDSNNLGVVFGGGTQLTVLS SEQ ID NO:25,

PGIA-2-A12

QVQLQQSGAEVRKPGASVKISCKTSGYTFMDYYIHWVRQAPGQGLEWMGWSNPVTGT
SGSSPKFRGRVTLTTDTSGNTAYLDLRSLRSDDTAVFYCARRHQQSLDYWGQGTLVT
VSSGGGGSGGGGSGGGGSAQAVLTQPSSLSASPGASASLTCTLRSDINVGSYSINWY
QQKPGSPPQYLLNYRSDSDKQQGSGVPSRFSGSKDASANAGILLISGLQSEDEADYY
CMIWYRTAWVFGGGTKVTVLG SEQ ID NO:26,

PGIA-2-B1

QVQLVQSGAEVRKPGASVKVSCKTSGYTFIEYYIHWVRQAPGQGLEWMGWSNPVTGT
SGSSPKFRGRVTLTTDTSGNTAYLDLRSLRSDDTAVFYCARRHQQSLDYWGRGTTVT
VSSGGGGSGGGGSGGGGSAQSVLTQPPSVSAAPGQKVTISCSGTNSNIGNYYVSWYQ
QLPGTAPKLLIYDNNKRPSGVPDRFSGSKSGTSASLVISGLRSEDEADYYCAAWDGS
LTAWVFGGGTKVTVLG SEQ ID NO:27,

PGIA-3-A1

QVQLQESGPGLVKPSGTLSLTCAVSGDSISSSNWWTWVRQPPGKGLEWIGEIFHSGT
TNYNPSLNNRVTISLDESRNQFSLELSSVTAADTAIYYCARDSGNYDDNRGYDYWGR
GTLVTVSSGGGGSGGGGSGGGGSAQSVLTQPPSVSGAPGQRVTISCAGTSSNIGAGF
DVHWYQLLPGRAPKLLIYGNNNRPSGVPDRFSGSKSGTSASLAISGLQSEDEGDYYC
AAWDDTVGGPVFGGGTKLTVLG SEQ ID NO:28,

PGIA-3-A2

QVQLQESGPGLVKPSGTLSLTCAVSGGSISSTNWWSWVRQPPGKGLEWIGEIYHSGS
TNYNPSLKSRVTISVDKSKNHFSLNLSSVTAADTAVYYCARDSMGSTGWHYGMDLWG
RGTLVTVSSGGGGSGGGGSGGGGSAQSALTQPAAVSGSPGQSITISCTGSSSDVGGY
NYVSWYQQHPGKAPKLLIYDVSDRPSGVSYRFSGSKSGNTASLTISGLQAEDEADYY
CSSYTATGTLVFGGGTKLTVLG SEQ ID NO:29,

PGIA-3-A3

QVQLQESGPGLVKPSGTLSLTCAVSGGSISSTNWWSWVRQPPGKGLEWIGEIYHSGS
TNYNPSLKSRVTISVDKSKNHFSLNLSSVTAADTAVYYCARDSMGSTGWHYGMDLWG
QGTTVTVSSGGGGSGGGGSGGGGSAQSALTQPASVSGSPGQSITISCTGTSSDVGGY
NYVSWYQQHPGKAPKLMIYEVSNRPLGVSNRFSGSKSGNTASLTISGLQAEDEGDYY
CSSYTSSTTLIVFGGGTKLTVLG SEQ ID NO:30,

PGIA-3-A4

QVQLQESGPGLVKPSGTLSLTCAVSGGSISTSDWWSWVRRPPGKGLEWIGEIYHSGS
TNYHPSLKSRVTISLDKSKNQFSLKLSSVTAADTAVYYCAREGGHSGSYPLDYWGQG
TLVTVSSGGGGSGGGGSGGGGSAQSVLTQPPSVSGTTGQRVILSCSGGNSNIGYNSV
NWYQQLPGTAPKLLIYTDDQRPSGVPDRFSGSRSGTSASLAISGLQSEDEADYYCAT
WDDSLNAGVFGGGTKLTVLG SEQ ID NO:31,

PGIA-3-A5

QVQLVQSGAEVRKPGASVRVSCKTSGYTFLEYYIHWVRQAPGQGLEWMAWSNPVTGT
SGSSPKFRGRVTLTADTSGNTAYLDLKSLTSDDTAIFYCARRHQQSLDYWGQGTLVT
VSSGGGGSGGGGSGGGGSAQSVLTQPPSVSAAPGQTVTISCSGSNSNIGNNHVSWYR
QLPETAPKLLIYDNNKRPSGIPDRFSGSKSGTSATLDITGLQTGDEADYYCATWDNS
LSAPWVFGGGTKLTVLG SEQ ID NO:32,

PGIA-3-A6

QVQLQESGAEVKKPGSSVKVSCKASGGTFSSSAISWVRQAPGQGLEWMGGIIPVFGT
ANYAQKFQDRVTITADESTSTAYLELSRLTSEDTAVYYCASRGEYDYGDYDVYYYYM
EVWGQGTLVTVSSGGGGSGGGGSGGGGSAQSVLTQPPSVSVAPGQTARLTCGANNIG
STSVHWYQQKPGQAPVLVIYDDTDRPSGIPERFSGSNSGNTATLTIRRVEAGDEADY
YCQVWDTNSDHVIFGGGTKLTVLG SEQ ID NO:33,

PGIA-3-A7

EVQLVQSGAEVKKPGSSVKVSCQASGGTFTSHAMYWVRQAPGQGLEWMGGIIPIFGR
TNYAQKFQGRVTFTADMSTSTAYMEMTSLRSDDTAVYYCARGDNWNDLYPIDYWGRG
TLVTVSSGGGGSGGGGSGGGGSALNFMLTQPHSVSESPGKTVTISCTRSSGSIATTY
VQWFQQRPGSSPTTVIYDDDQRPSGVPDRFSGSIDSSSNSASLTISGLMPEDEADYY
CQSYDNTDLVFGGGTQLTVLS SEQ ID NO:34,

PGIA-3-A8

EVQLVQSGAEVKKPGASVKVSCKVSGYSLSELSMHWVRQAPGKGLEWMGGFDPQNGY
TIYAQEFQGRITMTEDTSTDTVYMELGSLRSEDTAVYFCAAIEITGVNWYFDLWGKG
TLVTVSSGGGGSGGGGSGGGGSALSSELTQDPDVSVALGQTVRITCQGDSLKKFYPG
WYQQKPGQAPLLVLYGENIRPSRIPDRFSGSSSGNTATLTITGAQAEDEAVYYCNSR
EASVHHVRVFGGGTKLTVLG SEQ ID NO:35,

PGIA-3-A9

QVQLQESGPGLVKPSGTLSLTCAVSGGSISTSDWWSWVRRPPGKGLEWIGEIYHSGS
TNYHPSLKSRVTISLDKSKNQFSLKLSSVTAADTAVYYCAREGGHSGSYPLDYWGKG
TLVTVSSGGGGSGGGGSGGGGSALNFMLTQPHSVSESPGKTVTISCTRSSGSIASNY
VQWYQQRPGSSPTTVIYEDNQRPSGVPDRFSGSIDSSSNSASLTISGLKTEDEADYY
CQSYDSSNQGVVFGGGTKLTVLG SEQ ID NO:36,

PGIA-3-A10

QLQLQESGPGLVKPSGTLSLTCAVSGGSISTSDWWSWVRRPPGKGLEWIGEIYHSGS
TNYHPSLKSRVTISLDKSKNQFSLKLSSVTAADTAVYYCAREGGHSGSYPLDYWGQG
TLVTVSSGGGGSGGGGSGGGGSALNFMLTQPHSVSESPGKTVTISCTGSSGSIASNY
VQWYQQRPGSAPTTLIYEDDQRPSGVPDRFSGSVDSSSNSASLTISGLKTEDEADYY
CQSYDRSNQAVVFGGGTKLTVLG SEQ ID NO:37,

PGIA-3-A11

QVQLVQSGPEVKKPGASVEVSCKASGYTFTGDYMHWVRQAPGQGPEWMGWINPQTGV
TKYAQKFQGRVTMARDTSINTAYMELRGLRSDDTAVYYCVREDHNYDLWSAYNGLDV
WGQGTLVTVSSGGGGSGGGGSGGGGSAQSVLTQPPSVSAAPGQKVTISCSGSSSNIG
NNHVSWYQQLAGTAPKLLIFDNDKRPSGIPDRFSGSKSGTSATLGITGLQTGDEADY
YCGTWDKSPTDIYVFGSGTKLTVLG SEQ ID NO:38,

PGIA-3-A12

QVQLQESGPGLVKPSGTLSLTCAVSGGSISSSNWWSWVRQAPGKGLEWIGEIYYGGS
TNYNPSLKSRVTLSVDKSKNQFSLRLISVTAADTAVYYCARSSGLYGDYGNLWGRGT
LVTVSSGGGGSGGGGSGGGGSAQSVVTQPPSVSAAPGQKVTISCSGSASNIGDHYIS
WYQQFPGTAPKLLISDNDQRPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTW
DSNLSSWVFGSGTKVTVLG SEQ ID NO:39,

PGIA-3-B1

EVQLVQSGAEVKKPGATLKVSCKVSAYTFTDYSMHWVQQAPGKGLKWMGLIDLEDGN
TIYAEEFQDRVTITADTSTDTAYMDLSSLRSEDTAVFYCAISPLRGLTADVFDVWGQ
GTLVTVSSGGGGSGGGGSGGGGSAQSALTQPASASGSPGQSITISCTGTSSDIGRYD
FVSWYQRQPGKAPKLMIYDVINRPSGVSSRFSGSKSGNTASLTISGLQAEDEADYYC
SSYAGSTTLYVFGTGTKLTVLG SEQ ID NO:40,

PGIA-3-B2

QVQLQESGPGLVKPSATLSLTCAVSGGSISSNHWWSWVRQSPGKGLEWIGEIYTYGG
ANYNPSLKSRVDISMDKSKNQFSLHLSSVTAADTAVYYCGRHLTGYDCFDIWGQGTL
VTVSSGGGGSGGGGSGGGGSAQAVLTQPSSVSGAPGQRVTISCTGSSSNIGAGYDVH
WYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYYCQSY
DSSLSGVFGTGTQLTVLS SEQ ID NO:41,

PGIA-3-B3

QVQLQESGPGLVKPSGTLSLTCAVSGGSISTSDWWSWVRRPPGKGLEWIGEIYHSGS
TNYHPSLKSRVTISLDKSKNQFSLKLSSVTAADTAVYYCAREGGHSGSYPLDYWGQG
TLVTVSSGGGGSGGGGSGGGGSALNFMLTQPHSVSESPGKTVTISCTRSSGSIASKY
VQWYQQRPGSAPTSVIYEDNQRPSGVPDRFSGSIDSASNSASLTISGLKTEDEADYY
CQSDDGSSVVFGGGTKVTVLG SEQ ID NO:42,

PGIA-3-B4

EVQLVQSGAEVKKPGASVKVSCKASGYSFPSSGLSWVRQAPGQGPEWMGWIGIYNGN
TDYAQKFQGRVTMTTDKSTSTAYMELRSLRSDDTAVYYCARDSVGSISVAGTMQYYY

FAMDVWGQGTLVTVSSGGGGSGGGGSGGGGSAQSVLTQPPSASGSPGQSVTISCAGT
RYDIGTYNYVSWYQQHPAKGPKLIIYAVSERPSGVPNRFSGSKSGNTASLTVSGLRA
EDEAHYYCSSYAGNNNVIFGGGTKVTVLG SEQ ID NO:43,

PGIA-3-B5

QVQLQESGPGLVKPSGTLSLTCAVSGGSISTSDWWSWVRRPPGKGLEWIGEIYHSGS
TNYHPSLKSRVTISLDKSKNQFSLKLSSVTAADTAVYYCAREGGHSGSYPLDYWGRG
TMVTVSSGGGGSGGGGSGGGGSAQSVLTQPPSASGTPGQRVTISCSGSFSNIGGNYV
NWYQQLPGTAPKLLIYGNNQRPSGVPDRFSSFKSGTSASLAISGLRSEDEADYYCAT
WDDSQTVLFGGGTKLTVLG SEQ ID NO:44,

PGIA-3-B6

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGS
TYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARWNGFLTAHDSWGRGTM
VTVSSGGGGSGGGGSGGGGSAQSVLTQPPSASGTPGQRVTISCSGSSSNIGTNYVYW
YQQFPGTAPKLLIYRSNRRPSGVPDRFSASKSGTSASLVISGLRSEDEADYYCAAWD
DRLNGEMFGGGTKVTVLG SEQ ID NO:45,

PGIA-3-B7

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGS
TYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARWSGRFYDFWGQGTTVT
VSSGGGGSGGGGSGGGGSAQSVLTQPPSASGTPGQRITISCSGSSSNIGSNYVYWYQ
QLPGTAPKILIYRNNQRPSGVPERFSGSKSGTSASLAISGLRSEDEADYYCAAWDDS
LSEVFGGGTKVTVLG SEQ ID NO:46,

PGIA-3-B8

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGS
TYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDKGYSGFDYWGRGTLV
TVSSGGGGSGGGGSGGGGSAQSVLTQPPSASGTPGQRVTISCSGSSSNIGRHTVNWY
QQLPGTAPKLLIYSNNQRPSGVPDRFSGSKSGTSASLAISGLQSEDEGHYHCAAWDD
TLNGDVVFGGGTKVTVLG SEQ ID NO:47

PGIA-4-A1

QLQLQESGPGLVKPSGTLSLTCAVSGGSISTSDWWSWVRRPPGKGLEWIGEIYHSGS
TNYHPSLKSRVTISLDKSKNQFSLKLSSVTAADTAVYYCAREGGHSGSYPLDYWGKG
TLVTVSSGGGGSGGGGSGGGGSALNFMLTQPHSVSESPGKTVTISCTRSSGSIASNY
VQWYQQRPGSSPTTVIYEDNQRPSGVPDRFSGSIDSSSNSASLTISGLKTEDEADYY
CQSYDSSNPYVVFGGGTKLTVLG SEQ ID NO:48,

PGIA-4-A2

QVQLQESGPGLVKPSGTLSLTCAVSGGSISTSDWWSWVRRPPGKGLEWIGEIYHSGS
TNYHPSLKSRVTISLDKSKNQFSLKLSSVTAADTAVYYCAREGGHSGSYPLDYWGQG
TLVTVSSGGGGSGGGGSGGGGSALNFMLTQPHSVSGSPGRTVTISCTRSSGSIATNY

VQWYQQRPGSSPTIVIYEDNQRPSGVPDRFSGSIDTSSNSASLTISGLKTEDEADYY
CQSYDSNNLGVVFGGGTQLTVLS SEQ ID NO:49,

PGIA-4-A3

QLQLQESGPGLVKPSGTLSLTCAVSGGSISTSDWWSWVRRPPGKGLEWIGEIYHSGS
TNYHPSLKSRVTISLDKSKNQFSLKLSSVTAADTAVYYCAREGGHSGSYPLDYWGQG
TLVTVSSGGGGSGGGGSGGGGSAQSVVTQPPSVSAAPGQKVTISCSGSSSNIGNNYV
SWYKQLPGTAPKLLIYDNNKRPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGT
WDSSLSGVVFGGGTKLTVLG SEQ ID NO:50,

PGIA-4-A4

QLQLQESGPGLVKPSGTLSLTCAVSGGSISTSDWWSWVRRPPGKGLEWIGEIYHSGS
TNYHPSLKSRVTISLDKSKNQFSLKLSSVTAADTAVYYCAREGGHSGSYPLDYWGRG
TLVTVSSGGGGSGGGGSGGGGSALNFMLTQPHSVSESPGKTVTISCTRSSGSIASNY
VQWYQQRPGSSPTTLIYDDNQRPSGVPDRFSGSIDSSSNSASLTISGLKTEDEADYY
CQSYDSSNLGVVFGGGTKLTVLG SEQ ID NO:51,

PGIA-4-A5

QVQLQESGPGLVKPSGTLSLTCAVSGGSISTSDWWSWVRRPPGKGLEWIGEIYHSGS
TNYHPSLKSRVTISLDKSKNQFSLKLSSVTAADTAVYYCAREGGHSGSYPLDYWGRG
TLVTVSSGGGGSGGGGSGGGGSALNFMLTQPHSVSESPGKTATISCTGSGGSIARSY
VQWYQQRPGRAPSIVIYEDYQRPSGVPDRFSGSIDSSSNSASLTITGLKTDDEADYY
CQSSDDNNNVVFGGGTKVTVLG SEQ ID NO:52,

PGIA-4-A6

QVQLQESGPGLVKPSGTLSLTCAVSGGSISTSDWWSWVRRPPGKGLEWIGEIYHSGS
TNYHPSLKSRVTISLDKSKNQFSLKLSSVTAADTAVYYCAREGGHSGSYPLDYWGRG
TLVTVSSGGGGSGGGGSGGGGSAQAVLTQPSSVSAAPGQKVTISCSGSSSNIGNNYV
SWYQQLPGTAPKLLIYDNNERPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGT
WDSSLSTVVFGTGTKVTVLG SEQ ID NO:53,

PGIA-4-A7

QLQLQESGPGLVKPSGTLSLTCAVSGGSISTSDWWSWVRRPPGKGLEWIGEIYHSGS
TNYHPSLKSRVTISLDKSKNQFSLKLSSVTAADTAVYYCAREGGHSGSYPLDYWGQG
TLVTVSSGGGGSGGGGSGGGGSALNFMLTQPHSVSESPGKTVTVSCTGSGGNIASNY
VQWYQQRPDSAPTLVIFEDTQRPSGVPARFSGSIDSSSNSASLIISSLRTEDEADYY
CQSSDSNRVVFGGGTKVTVLG SEQ ID NO:54,

PGIA-4-A8

QVQLQESGPGLVKPSETLSLTCNVSGGSIRNYFWSWIRQPPGQGLEYIGYIYYSGTT
DYNPSLKGRVTISLDTSKTQFSLKLNSVTAADTAFYYCVRGPNKYAFDPWGQGTLVT
VSSGGGGSGGGGSGGGGSALSYELTQPPSVSVSPGQTASITCSGDKLGDKFASWYQQ
KAGQSPVLVIYRDTKRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCQAWDSST
AVFGTGTKVTVLG SEQ ID NO:55,

PGIA-4-A9

QLQLQESGPGLVKPSGTLSLTCAVSGGSISTSDWWSWVRRPPGKGLEWIGEIYHSGS
TNYHPSLKSRVTISLDKSKNQFSLKLSSVTAADTAVYYCAREGGHSGSYPLDYWGQG
TLVTVSSGGGGSGGGGSGGGGSALNFMLTQPHSVSESPGKTVTISCTRSSGSIDNNY
VQWYQQRPGSSPTTVIFEDNQRPSGVPDRFSGSIDSSSNSASLTISGLKTEDEADYY
CQSYDSHNQGVVFGGGTKLTVLG SEQ ID NO:56

PGIA-4-A10

QLQLQESGPGLVKPSGTLSLTCAVSGGSISTSDWWSWVRRPPGKGLEWIGEIYHSGS
TNYHPSLKSRVTISLDKSKNQFSLKLSSVTAADTAVYYCAREGGHSGSYPLDYWGRG
TLVTVSSGGGGSGGGGSGGGGSAQSVLTQPPSVSAAPGQKVTISCSGSSSNIGNSYV
SWYKQLPGTAPKVLIYDNQKRSSGIPDRFSASKSGTSATLGITGLRTEDEADYYCGT
WDTSLSAVVFGGGTKLTVLG SEQ ID NO:57,

PGIA-4-A11

EVQLVESGPGLVKPSGTLSLTCAVSGGSISTSDWWSWVRRPPGKGLEWIGEIYHSGS
TNYHPSLKSRVTISLDKSKNQFSLKLSSVTAADTAVYYCAREGGHSGSYPLDYWGRG
TLVTVSSGGGGSGGGGSGGGGSAQSVVTQPPSVSAAPGQKVTISCSGNFSNIEYNYV
SWYQHLPGTAPKLLIFDNNQRPSWIPDRFSGSKSGTSATLGITGLQTGDEADYYCGT
WDSSLNAGVFGGGTKVTVLG SEQ ID NO:58,

PGIA-4-A12

EVQLLESGGGLVRPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGS
TYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDRRGVLDPWGKGTMVT
VSSGGGGSGGGGSGGGGSAQSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWY
QHLPGTAPRLLIYGNSNRPSGVPDRFSGSKSGTSASLAISGLQAEDEADYYCQSYDS
SLSDWVFGGGTKVTVLG SEQ ID NO:59, and

PGIA-5A1

QLQLQESGPGLVKPSGTLSLTCAVSGGSISTSDWWSWVRRPPGKGLEWIGEIYHSGS
TNYHPSLKSRVTISLDKSKNQFSLKLSSVTAADTAVYYCAREGGHSGSYPLDYWGRG
TLVTVSSGGGGSGGGGSGGGGSALNFMLTQPHSVSESPGKTVTISCARSSGSIASNY
VQWYQQRPGSSPTTLIYEDRQRPSGVPDRFSGSIDSSSNSASLTISGLKTEDEADYY
CQSYDSSDHVVFGGGTKLTVLG SEQ ID NO:60.

[0097] In another preferred embodiment, the c-Met antibody comprises a light chain amino acid sequence from SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19,

SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, or SEQ ID NO:60, or one or more CDRs from these amino acid sequences. In another preferred embodiment, the c-Met antibody comprises a heavy chain amino acid sequence from SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, or SEQ ID NO:60 or one or more CDRs from these amino acid sequences.

Class and Subclass of C-Met Antibodies

[0098] The antibody may be an IgG, an IgM, an IgE, an IgA, or an IgD molecule. In a preferred embodiment, the antibody is an IgG and is an IgG1, IgG2, IgG3, or IgG4 subtype. In a more preferred embodiment, the c-Met antibody is subclass IgG1. In another preferred embodiment, the c-Met antibody is the same class and subclass as antibody PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-

02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, or PGIA-05-A1, which is IgG1.

[0099] The class and subclass of c-Met antibodies may be determined by any method known in the art. In general, the class and subclass of an antibody may be determined using antibodies that are specific for a particular class and subclass of antibody. Such antibodies are available commercially. The class and subclass can be determined by ELISA, Western Blot, as well as other techniques.

[00100] Alternatively, the class and subclass may be determined by sequencing all or a portion of the constant domains of the heavy and/or light chains of the antibodies, comparing their amino acid sequences to the known amino acid sequences of various class and subclasses of immunoglobulins, and determining the class and subclass of the antibodies.

Molecule Selectivity

[00101] In another embodiment, the c-Met antibody has a selectivity for c-Met that is at least 50 times greater than its selectivity for IGF-1R, insulin, Ron, Axl, and Mer receptors. In a preferred embodiment, the selectivity of the c-Met antibody is more than 100 times greater than for IGF-1R, insulin, Ron, Axl, and Mer receptors. In an even more preferred embodiment, the c-Met antibody does not exhibit any appreciable specific binding to any other protein than c-Met. One may determine the selectivity of the c-Met antibody for c-Met using methods well known in the art following the teachings of the specification. For instance, one may determine the selectivity using Western blot, FACS, ELISA, or RIA. In a preferred embodiment, one may determine the molecular selectivity using Western blot.

Binding Affinity of c-Met antibody to c-Met

[00102] In another aspect of the invention, the c-Met antibodies bind to c-Met with high affinity. In one embodiment, the c-Met antibody binds to c-Met with a K_d of 1 x 10^{-8} M or less. In a more preferred embodiment, the antibody binds to c-Met with a K_d or 1 x 10^{-9} M or less. In an even more preferred embodiment, the antibody binds to c-Met with a K_d or 5 x 10^{-10} M or less. In another preferred embodiment, the antibody binds to c-Met with a K_d of 1 x 10^{-10} M or less. In another preferred embodiment, the antibody binds to c-Met with substantially the same K_d as an antibody selected from PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, and PGIA-05-A1. In another preferred embodiment, the antibody binds to c-Met with substantially the same K_d as an antibody that comprises one or more CDRs from an antibody selected from PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, and PGIA-05-A1. In still another preferred embodiment, the antibody binds to c-Met with substantially the same K_d as an antibody that comprises one of the amino acid sequences selected from SEQ ID NO:1,

SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, and SEQ ID NO:60. In another preferred embodiment, the antibody binds to c-Met with substantially the same K_d as an antibody that comprises one or more CDRs from an antibody that comprises one of the amino acid sequences selected from SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, and SEQ ID NO:60.

[00103] In another aspect of the invention, the c-Met antibody has a low dissociation rate. In one embodiment, the c-Met antibody has a K_{off} of 1×10^{-1} s^{-1} or lower. In a preferred embodiment, the K_{off} is 5×10^{-5} s^{-1} or lower. In another preferred embodiment, the K_{off} is substantially the same as an antibody selected from PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-

01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, and PGIA-05-A1. In another preferred embodiment, the antibody binds to c-Met with substantially the same K_{off} as an antibody that comprises one or more CDRs from an antibody selected from PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, and PGIA-05-A1. In still another preferred embodiment, the antibody binds to c-Met with substantially the same K_{off} as an antibody that comprises one of the amino acid sequences selected from SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID

NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, and SEQ ID NO:60. In another preferred embodiment, the antibody binds to c-Met with substantially the same K_{off} as an antibody that comprises one or more CDRs from an antibody that comprises one of the amino acid sequences selected from SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, and SEQ ID NO:60 or a fragment thereof.

[00104] The binding affinity and dissociation rate of a c-Met antibody to c-Met may be determined by any method known in the art. In one embodiment, the binding affinity can be measured by competitive ELISAs, RIAs, or surface plasmon resonance, such as BIAcore. The dissociation rate can also be measured by surface plasmon resonance. In a more preferred embodiment, the binding affinity and dissociation rate is measured by surface plasmon resonance. In an even more preferred embodiment, the binding affinity and dissociation rate is measured using a BIAcore. An example of determining binding affinity and dissociation rate for binding of c-Met antibodies to the extracellular domain of human c-Met using BIAcore is described below in Example 10.

Half-Life c-Met Antibodies

[00105] According to another object of the invention, the c-Met antibody has a half-life of at least one day *in vitro* or *in vivo*. In a preferred embodiment, the antibody or portion thereof has a half-life of at least three days. In a more preferred

embodiment, the antibody or portion thereof has a half-life of four days or longer. In another embodiment, the antibody or portion thereof has a half-life of eight days or longer. In another embodiment, the antibody or antigen-binding portion thereof is derivatized or modified such that it has a longer half-life, as discussed below.

[00106] In another preferred embodiment, the antibody may contain point mutations to increase serum half-life, such as described WO 00/09560, published February 24, 2000.

[00107] The antibody half-life may be measured by any means known to one having ordinary skill in the art. For instance, the antibody half-life may be measured by Western blot, ELISA or RIA over an appropriate period of time. The antibody half-life may be measured in any appropriate animals, e.g., a monkey, such as a cynomolgus monkey, a primate or a human.

[00108] The invention also provides a c-Met antibody that binds the same antigen or epitope as a human c-Met antibody of the present invention. Further, the invention provides a c-Met antibody that cross-competes with a c-Met antibody known to block HGF binding. In a highly preferred embodiment, the known c-Met antibody is another human antibody. In a preferred embodiment, the human c-Met antibody has the same antigen or epitope of PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, or PGIA-05-A1. In another preferred embodiment, the human c-Met antibody comprises one or more CDRs from an antibody that binds the same antigen or epitope selected from PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-

A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, and PGIA-05-A1. In still another preferred embodiment, the human c-Met antibody that binds the same antigen or epitope comprises one of the amino acid sequences selected from SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, and SEQ ID NO:60 or a fragment thereof. In another preferred embodiment, the human c-Met antibody that binds the same antigen or epitope comprises one or more CDRs from an antibody of the amino acid sequences selected from SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50,

SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, and SEQ ID NO:60.

[00109] One may determine whether a c-Met antibody binds to the same antigen using a variety of methods known in the art. For instance, one may determine whether a test c-Met antibody binds to the same antigen by using a c-Met antibody to capture an antigen that is known to bind to the c-Met antibody, such as c-Met, eluting the antigen from the antibody, and determining whether the test antibody will bind to the eluted antigen. One may determine whether the antibody binds to the same epitope as a c-Met antibody by binding the c-Met antibody to c-Met under saturating conditions, and then measuring the ability of the test antibody to bind to c-Met. If the test antibody is able to bind to the c-Met at the same time as the c-Met antibody, then the test antibody binds to a distinct epitope from the c-Met antibody. However, if the test antibody is not able to bind to the c-Met at the same time, then the test antibody binds to the same epitope, or shares an overlapping epitope binding site, as the human c-Met antibody. This experiment may be performed using ELISA, RIA, or surface plasmon resonance. In a preferred embodiment, the experiment is performed using surface plasmon resonance. In a more preferred embodiment, BIAcore is used. One may also determine whether a c-Met antibody cross-competes with another c-Met antibody. In a preferred embodiment, one may determine whether a c-Met antibody cross-competes with another by using the same method that is used to measure whether the c-Met antibody is able to bind to the same epitope as another c-Met antibody.

Light and Heavy Chain Usage

[00110] The invention also provides a c-Met antibody that comprises variable sequences encoded by a human λ or κ gene. In a preferred embodiment, the light chain variable sequences are encoded by the Vλ 1e, 1b, 3r, or 6a gene family. In one embodiment, the variable sequences are encoded by the Vκ A27, A30, or O12 gene family. In a more preferred embodiment, the light chain comprises no more than ten amino acid substitutions from the germline, preferably no more than six amino acid substitutions, and more preferably no more than three amino acid substitutions. In a preferred embodiment, the amino acid substitutions are conservative substitutions.

[00111] SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, and SEQ ID NO:60 provide the amino acid sequences of the variable regions of c-Met antibody λ light chains. Following the teachings of this specification, one of ordinary skill in the art could determine the encoded amino acid sequence of the c-Met antibody light chains and the germline light chains and determine the differences between the germline sequences and the antibody sequences.

[00112] In a preferred embodiment, the VL of the c-Met antibody contains the same amino acid substitutions, relative to the germline amino acid sequence, as any one or more of the VL of antibodies PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, or PGIA-05-A1. For example, the VL of the c-Met antibody may contain one or more amino acid substitutions that are the same as those present in antibody PGIA-03-A9, another amino acid substitution that is the same as that present in antibody PGIA-03-B2, and another amino acid substitution

that is the same as antibody PGIA-01-A8. In this manner, one can mix and match different features of antibody binding in order to alter, e.g., the affinity of the antibody for c-Met or its dissociation rate from the antigen. In another embodiment, the amino acid substitutions are made in the same position as those found in any one or more of the VL of antibodies PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, and PGIA-05-A1, but conservative amino acid substitutions are made rather than using the same amino acid. For example, if the amino acid substitution compared to the germline in one of the antibodies PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, and PGIA-05-A1 is glutamate, one may conservatively substitute aspartate.

[00113] Similarly, if the amino acid substitution is serine, one may conservatively substitute threonine. In another preferred embodiment, the light chain comprises an amino acid sequence that is the same as the amino acid sequence of the VL of PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12,

PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, or PGIA-05-A1. In another highly preferred embodiment, the light chain comprises amino acid sequences that are the same as the CDR regions of the light chain of PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, and PGIA-05-A1. In another preferred embodiment, the light chain comprises an amino acid sequence from at least one CDR region of the light chain of PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, and PGIA-05-A1. In another preferred embodiment, the light chain

comprises amino acid sequences from CDRs from different light chains. In a more preferred embodiment, the CDRs from different light chains are obtained from PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, and PGIA-05-A1. In another preferred embodiment, the light chain comprises a VL amino acid sequence selected from SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, and SEQ ID NO:60. In another embodiment, the light chain comprises an amino acid sequence encoded by a nucleic acid sequence selected from SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID

NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, and SEQ ID NO:120, fragments thereof, or a nucleic acid sequence that encodes an amino acid sequence having 1-10 amino acid insertions, deletions or substitutions therefrom. Preferably, the amino acid substitutions are conservative amino acid substitutions. In another embodiment, the antibody or portion thereof comprises a lambda light chain.

[00114] The present invention also provides a c-Met antibody or portion thereof, which comprises a human heavy chain or a sequence derived from a human heavy chain. In one embodiment, the heavy chain amino acid sequence is derived from a human V_H DP-35, DP-47, DP-70, DP-71, or VIV-4/4.35 gene family. In a more preferred embodiment, the heavy chain comprises no more than eight amino acid changes from germline, more preferably no more than six amino acid changes, and even more preferably no more than three amino acid changes.

[00115] SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, and SEQ ID NO:60 provide the amino acid sequences of the variable regions of c-Met antibody heavy chains. Following the teachings of this specification, one of ordinary skill in the art could determine the encoded amino acid sequence of the c-Met antibody heavy chains

and the germline heavy chains and determine the differences between the germline sequences and the antibody sequences.

[00116] In a preferred embodiment, the VH of the c-Met antibody contains the same amino acid substitutions, relative to the germline amino acid sequence, as any one or more of the VH of antibodies PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, and PGIA-05-A1. Similar to what was discussed above, the VH of the c-Met antibody may contain one or more amino acid substitutions that are the same as those present in antibody PGIA-03-A9, another amino acid substitution that is the same as that present in antibody PGIA-03-B2, and another amino acid substitution that is the same as antibody PGIA-01-A8. In this manner, one can mix and match different features of antibody binding in order to alter, e.g., the affinity of the antibody for c-Met or its dissociation rate from the antigen. In another embodiment, the amino acid substitutions are made in the same position as those found in any one or more of the VH of antibodies PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, and

PGIA-05-A1, but conservative amino acid substitutions are made rather than using the same amino acid.

[00117] In another preferred embodiment, the heavy chain comprises an amino acid sequence that is the same as the amino acid sequence of the VH of PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, or PGIA-05-A1. In another highly preferred embodiment, the heavy chain comprises amino acid sequences that are the same as the CDR regions of the heavy chain of PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, or PGIA-05-A1. In another preferred embodiment, the heavy chain comprises an amino acid sequence from at least one CDR region of the heavy chain of PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2,

PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, or PGIA-05-A1. In another preferred embodiment, the heavy chain comprises amino acid sequences from CDRs from different heavy chains. In a more preferred embodiment, the CDRs from different heavy chains are obtained from PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, and PGIA-05-A1. In another preferred embodiment, the heavy chain comprises a VH amino acid sequence selected from SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, and SEQ ID NO:60. In another embodiment, the heavy chain comprises a VH amino acid sequence encoded by a nucleic acid sequence selected

from SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, and SEQ ID NO:120, a fragment thereof, or a nucleic acid sequence that encodes an amino acid sequence having 1-10 amino acid insertions, deletions or substitutions therefrom. In another embodiment, the substitutions are conservative amino acid substitutions.

[00118] Table 2 shows a nucleic acid sequences encoding the scFvs PGIA-01-A1 through PGIA-05-A1.

TABLE 2

PGIA-01-A1
GAGGTGCAGCTGTTGGAGTCTGGGCGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGA
CTCTCCTGTGCAGCCTCTGGATTCACCTTTAGCAGCTATGCCATGAGCTGGGTCCGC
CAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGCTATTAGTGGTAGTGGTGGTAGC
ACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAG
AACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTAC
TGTGCGAGATTTGCCGTAACTGGGGAGTTTGACTACTGGGGGCAGGGGACCACGGTC
ACCGTCTCGAGTGGAGGCGGCGGTTCAGGCGGAGGTGGCTCTGGCGGTGGCGGAAGT
GCACAGGCTGTGCTGACTCAGCCGTCCTCAGTGTCTGGGGCCCCAGGGCAGAGGGTC
ACCATCTCCTGCACTGGGAGCAGCTCCAACATCGGGGCAGATTATGATGTACACTGG
TACCAGCAGCTTCCAGGAACAGCCCCCAAACTCCTCATCTATGGTAACAACAATCGG
CCCTCAGGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTG
GCCATCACTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGCCAGTCCTATGAC
AACAGCCCGGATGCCTATGTGGTCTTCGGCGGAGGGACCAAGCTGACCGTCCTAAGT
SEQ ID NO:61,

PGIA-01-A2
CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAGAAAGCCTGGGGCCTCAGTGAAG
GTCTCCTGCAAGACTTCTGGATACACCTTCATCGACTACTATATACACTGGGTGCGA
CAGGCCCCTGGACAAGGGCTTGAGTGGATGGGCTGGGTCAACCCTGTCACTGGAACC
TCAGGCTCTTCACCCAACTTTCGGGGCAGGGTCACCATGACCACCGACACGTCCGGC
AACACAGCCTATATGGAACTGAGGAGCCTTAGATCTGACGACACGGCCGTATTTTAC
TGTGCGAGGCGTCACCAACAGAGCTTGGATTATTGGGGCCAGGGAACCCTGGTCACC
GTCTCGAGTGGAGGCGGCGGTTCAGGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGCA
CAGTCTGTGTTGACGCAGCCGCCCTCAGTGTCTGCGCCCCCGGGACAGAAGGTCACC
ATCTCCTGCTCTGGAAGCAGCTCCAACATTGGGACTAATTATGTATCCTGGTACCAG
CAGCTCCCAGGAACAGCCCCCAAACTCCTCATTTATGACAATCATAAGCGACCCTCA
GTGATTCCTGACCGCTTCTCTGGCTCCAAGTCTGGCACGTCAGCCACCCTGGGCATC
TCCGGACTCCAGACTGGGGACGAGGCCGATTATTACTGCGGAACATGGGATTACAGC
CTGAGTACTTGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTAGGT
SEQ ID NO:62,

PGIA-01-A3
CAGTTGCAGCTGCAGGAGTCCGGCCCAGGACTGGTGAAGCCTTCGGGGACCCTGTCC
CTCACCTGCGCTGTCTCTGGAGACTCCGTCAGCAGTTATTACTGGTGGAGTTGGGTC
CGCCAGCCCCCAGGGAAGGGGCTGGAGTGGATTGGAGAAATCTTTCGTGATGGGAGC
TCCAACTACAACCGGTCCCTCAAGAGTCGGGTCACCATATCCCCAGACAAGCCCAAG
AATCAGTTCTCTCTGAGGCTGAGCTCTGTGACCGCCGCGGACACGGCCATTTACTAC
TGTGCGAGGCATATACGCGGTTATGATGCTTTTGACATCTGGGGCCGGGGAACCCTG
GTCACCGTCTCGAGTGGAGGCGGCGGTTCAGGCGGAGGTGGCTCTGGCGGTGGCGGA
AGTGCACAGTCTGTGTTGACGCAGCCGCCCTCAGTGTCTGGGGCCCCAGGGCAGAGG
GTCACCATCTCCTGTACTGGGAGCAGCTCCAACATCGGGGCAGGTTATGATGTACAC
TGGTACCAGCAGTTTCCAGGAAGAGCCCCCAAGCTCCTCATCTATGGTAACACCAAT
CGGCCCTCAGGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGACATCTCAGCCTCC
CTGGCCATCACTGGGCTCCAGGCTGAGGATGAGGCTGATTATTACTGTCAGTCCTAT
GACAGCAACCTGACTGGGGTGTTCGGCGGAGGGACC SEQ ID NO:63,

PGIA-01-A4
CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAGGAAGCCTGGGGCCTCAGTGAAG
GTCTCCTGCAAGACTTCTGGATACACCTTCATGGACTACTACATACACTGGGTGCGA
CAGGCCCCTGGACAAGGGCTTGAGTGGATGGGCTGGAGCAACCCTGTCACTGGTACG
TCAGGCTCTTCACCTAAATTTCGGGGCAGGGTCACCTTGACCACTGACACGTCCGGC
AACACAGCCTATTTGGACCTGAGGAGCCTTAGATCTGACGACACGGCCGTATTTTAC
TGTGCGAGGCGTCACCAACAGAGCTTGGATTATTGGGGCCAAGGGACAATGGTCACC
GTCTCGAGTGGAGGCGGCGGTTCAGGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGCA
CAGTCTGTGTTGACGCAGCCGCCCTCAGTGTCTGCGGCCCCAGGACAGAAGGTCACC
ATCTCCTGCTCTGGAAGCAGCTCCAACATTGGGAATAATTATGTATCCTGGTACCAG
CAACTCCCAGGAACAGCCCCCAAACTCCTCATGTATGAAAATAGTAAGCGACCCTCA
GGGATTCCTGACCGGTTCTCTGGCTCCAAGTCTGGCACGTCAGGCACCCTGGGCATC
ACCGGACTCCAGACTGGGGACGAGGCCGATTATTACTGCGGAACATGGGATACCAGC
CTGAGAGCTTGGGTGTTCGGCGGAGGGACCAAGGTCACCGTCCTAGGT
SEQ ID NO:64,

PGIA-01-A5
CAGGTACAGCTGCAGCAGTCAGGGGCTGAGGTGAGGAAGCCTGGGGCCTCGGCGAAG
GTCTCCTGCAAGACTTCTGGATACACCTTCATCGACTACTATATACACTGGGTGCGA

CAGGCCCCTGGACAAGGGCTTGAGTGGATGGGCTGGATCAACCCTGTCACTGGTGCC
TCAGGCTCTTCACCTAACTTTCGGGGCAGGGTCACCTTGACCACCGACACGTCCGGC
AACACAGCCTATATGGAGCTGAGGAGCCTTAGATCTGACGACACGGCCGTGTTTTAC
TGTGCGAGGCGTCACCAACAGAGCTTGGATTATTGGGGGCGGGGGACCACGGTCACC
GTCTCGAGTGGAGGCGGCGGTTCAGGCGGAGGTGGCTCTGGCGGTGGCGGAAGTGCA
CAGTCTGTCGTGACGCAGCCGCCCTCAGTGTCTGCGGCTCCAGGACAGAAGGTCACC
ATCTCCTGCTCTGGGAGGACATCCAACATTGGGAACAATTATGTATCCTGGTATCAG
CAAGTCCCAGGAGCGCCCCCCAAACTACTCATTTTTGACAATAATAAGCGACCCTCA
GGGACTCCTGCCCGATTCTCTGGCTCCAAGTCTGGCACGTCAGCCACCCTGGCCATC
TCCGGACTCCAGACCGGGGACGAGGCCGATTATTACTGCGGAACATGGGATACTACC
CTGCGTGGTTTTGTCTTCGGGCCCGGGACCAAGGTCACCGTCCTAGGT
SEQ ID NO:65,

PGIA-01-A6
CAGCTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGGGACCCTGTCC
CTCACCTGCGCTGTCTCTGGTGGCTCCATCAGCAGTACTAACTGGTGGAGTTGGGTC
CGCCAGCCCCCAGGGAAGGGGCTGGAGTGGATTGGGGAAATCTATCATAGTGGGAGC
ACCAACTACAACCCGTCCCTCAAGAGTCGAGTCACCATATCAGTAGACAAGTCCAAG
AACCACTTCTCCCTGAACCTGAGCTCTGTGACCGCCGCGGACACGGCCGTGTATTAC
TGTGCGAGAGATTCTATGGGAAGCACTGGCTGGCATTACGGTATGGACCTCTGGGGC
CGGGGAACCCTGGTCACCGTCTCGAGTGGAGGCGGCGGTTCAGGCGGAGGTGGCTCT
GGCGGTGGCGGAAGTGCACAATCTGCCCTGACTCAGCCTCCCTCCGCGTCCGGGTCT
CCTGGACAGTCAGTCACCATCTCCTGCAGTGGAAGCAGTAGTGACATTGGTGATTAT
AACCATGTCTCCTGGTACCAACAGCACCCAGGCAAAGCCCCCAAACTCATGATTTAT
GACGTCAATAAGTGGCCCTCAGGGGTCCCTGATCGCTTCTCTGGCTCCAAGTCTGGC
AACACGGCCTCCCTGACCGTCTCTGGGCTCCAGGCTGAGGATGAGGCTGATTATTAT
TGCAGCTCATATTCAGGCATCTACAATTTGGTTTTCGGCGGAGGGACCAAGGTCACC
GTCCTAGGT SEQ ID NO:66,

PGIA-01-A7
GAGGTGCAGCTGGTGCAGTCTGGGGCTGAAGTGAAGAAGCCTGGGTCCTCGGTGAAG
GTCTCCTGTAAGGCCTCTGGAGGCACCTTCAAGACCTATGCTATCAATTGGGTGCGA
CAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAGGAATCATCCCTGTCCTGGGAACA
GCAAATTACGTTCAGAAGTTCCAGGGCAGAGTCACGATTACCGCGGACGAATCGACG
ACCACAGCCTACATGGAGCTGAGGGGCCTGAGATCTGAGGACACGGCCGTTTATTAT
TGTGCGAGAGGAGAGGGCAGTGGCTGGTACGATCACTACTACGGATTGGACGTCTGG
GGCCAAGGAACCCTGGTCACCGTCTCGAGTGGAGGCGGCGGTTCAGGCGGAGGTGGC
TCTGGCGGTGGCGGAAGTGCACAGTCTGTGCTGACGCAGCCGCCCTCAGCGTCTGGG
ACCCCCGGGCAGAGGGTCACCATCTCTTGTTCTGGAAGCAGCTCCAACATCGGAAGT
AATACTGTAAACTGGTACCGGCAGCTCCCAGGAACGGCCCCCAAACTCCTCATCTTT
GGTGATGATCAGCGGCCCTCAGGGGTCCCTGACCGATTCTCTGGCTCCAGGTCTGGC
ACCTCAGTCTCCCTGGCCATCAGTGGGCTCCAGTCTGAGGATGAGGCTGACTATTAC
TGTGCAGCATGGGATGACAGCCTGAATGGCGGGGTGTTCGGCGGAGGGACCAAGCTG
ACCGTCCTAGGT SEQ ID NO:67,

PGIA-01-A8
GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGA
CTCTCCTGTGCAGCCTCTGGATTCACCTTTAGCAGCTATGCCATGAGCTGGGTCCGC
CAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGCTATTAGTGGTAGTGGTGGTAGC
ACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATCTCCAGAGACAATTCCAAG

AACACGCTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCCGTGTATTAC
TGTGCGAAAGATCATTACTATGATAGTAGTGGTTATCTTGACTACTGGGGCCAAGGC
ACCCTGGTCACCGTCTCGAGTGGAGGCGGCGGTTCAGGCGGAGGTGGCTCTGGCGGT
GGCGGAAGTGCACTTAATTTTATGCTGACTCAGCCCCACTCTGTGTCGGAGTCTCCG
GGGAAGACGGTAACCATCTCCTGCACCCGCAGCAGTGGCAGCATTGCCTTCGACTAT
GTGCAGTGGTACCAGCAGCGCCCGGGCAGTGCCCCCACCACTGTGATCTATGAGGAT
AATCAAAGACCCTCTGGGGTCCCTGATCGGTTCTCTGCCTCCATCGACAGCTCCTCC
AACTCTGCCTCCCTCACCATCTCTGCACTGAAGACTGAGGACGAGGCTGACTACTAC
TGTCAGTCTTATGATAACAGCAATTCTTGGGTCTTCGGCGGAGGGACCAAGCTGACC
GTCCTAGGT SEQ ID NO:68,

PGIA-01-A9
AAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGGGTCCCTGAGA
CTCTCCTGTGCAGCCTCTGGATTCACCTTTAGCAGCTATGCCATGAGCTGGGTCCGC
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PGIA-01-A10
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SEQ ID NO:70,

PGIA-01-A11
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PGIA-01-A12
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ACCGTCCTAGGT SEQ ID NO:73

PGIA-01-B2
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SEQ ID NO:74,

PGIA-02-A1
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GGT SEQ ID NO:75,

PGIA-02-A2
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SEQ ID NO:76,

PGIA-02-A3
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PGIA-02-A4
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PGIA-02-A5
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SEQ ID NO:79,

PGIA-02-A6
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PGIA-02-A7
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PGIA-02-A8
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PGIA-02-A9
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PGIA-02-A10
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SEQ ID NO:84,

PGIA-02-A11
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PGIA-02-A12
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PGIA-02-B1
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SEQ ID NO:87,

PGIA-03-A1
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PGIA-03-A2
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PGIA-03-A3
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PGIA-03-A4
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PGIA-03-A5
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SEQ ID NO:92,

PGIA-03-A6
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PGIA-03-A7
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PGIA-03-A8
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PGIA-03-A9
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PGIA-03-A10
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PGIA-03-A11
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PGIA-03-A12
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SEQ ID NO:99,

PGIA-03-B1
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PGIA-03-B2
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SEQ ID NO:101,

PGIA-03-B3
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PGIA-03-B4
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PGIA-03-B5
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SEQ ID NO:104,

PGIA-03-B6
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SEQ ID NO:105,

PGIA-03-B7
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SEQ ID NO:106,

PGIA-03-B8
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SEQ ID NO:107,

PGIA-04-A1
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PGIA-04-A2
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PGIA-04-A3
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GGT SEQ ID NO:110

PGIA-04-A4
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ACCGTCCTAGGT SEQ ID NO:111

PGIA-04-A5
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GTGCAGTGGTACCAGCAGCGCCCGGGCCGTGCCCCCAGCATCGTTATCTATGAGGAT
TATCAAAGGCCCTCTGGCGTCCCTGATCGGTTCTCTGGCTCCATCGACAGCTCCTCC
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TGTCAGTCCTCTGACGACAACAACAATGTCGTCTTCGGCGGAGGGACCAAGGTCACC
GTCCTAGGT SEQ ID NO:112

PGIA-04-A6
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GGT SEQ ID NO:113,

PGIA-04-A7
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PGIA-04-A9
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ACCGTCCTAGGT SEQ ID NO:116,

PGIA-04-A10
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GGT SEQ ID NO:117,

PGIA-04-A11
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GGT SEQ ID NO:118,

PGIA-04-A12
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SEQ ID NO:119, and

PGIA-05-A1
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GTCCTAGGT SEQ ID NO:120.

Inhibition of c-Met Activity by c-Met antibody

Inhibition of HGF Binding to c-Met

[00119] In another embodiment, the invention provides c-Met antibodies that inhibit the binding of HGF to c-Met. In a preferred embodiment, the c-Met is of human origin. In another preferred embodiment, the c-Met antibody is a human antibody. In another embodiment, the antibody or portion thereof inhibits binding between c-Met and HGF with an IC_{50} of no more than 100 nM. In a preferred embodiment, the IC_{50} is no more than 10 nM. In a more preferred embodiment, the IC_{50} is no more than 5 nM. The IC_{50} can be measured by any of a number of methods known in the art. Typically, an IC_{50} can be measured by ELISA or RIA. In a preferred embodiment, the IC_{50} is measured by RIA.

[00120] In another embodiment, the invention provides a c-Met antibody that prevents activation of c-Met in the presence of HGF. In a preferred embodiment, the c-Met antibody inhibits c-Met-induced tyrosine phosphorylation of the kinase domain following receptor autophosphorylation. The c-Met antibody inhibits downstream cellular events from occurring. For instance, the c-Met antibody can inhibit serine phosphorylation of Akt that is normally phosphorylated and activated when cells are treated with HGF. One can determine whether a c-Met antibody can prevent activation of c-Met in the presence of HGF by determining the levels of tyrosine

phosphorylation for c-Met, or serine phosphorylation at Ser 473 on Akt by Western blot, immunoprecipitation, or ELISA assay.

[00121] In another aspect of the invention, the antibody causes the downregulation of c-Met from a cell treated with the antibody. In one embodiment, the c-Met is internalized into the endosomal pathway of the cell. After the c-Met antibody binds to c-Met, the antibody bound to c-Met is internalized. One may measure the downregulation of c-Met by any method known in the art including immunoprecipitation, confocal microscopy, or Western blot. In a preferred embodiment, the antibody is selected PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, and PGIA-05-A1, or comprises a heavy chain, light chain or antigen-binding region thereof.

Activation of c-Met by c-Met Antibody Binding

[00122] Another aspect of the present invention involves activating c-Met antibodies. An activating antibody differs from an inhibiting antibody because it amplifies or substitutes for the effects of HGF on c-Met. In one embodiment, the activating antibody is able to bind to c-Met and cause it to be activated in the absence of HGF. This type of activating antibody is essentially a partial or complete mimetic of HGF. In another embodiment, the activating antibody amplifies the effect of HGF on c-Met.

[00123] This type of antibody does not activate c-Met by itself, but rather increases the activation of c-Met in the presence of HGF. A mimic anti c-Met antibody may be easily distinguished from an amplifying c-Met antibody by treating cells *in vitro* with

an antibody in the presence or absence of low levels of HGF. If the antibody is able to cause c-Met activation in the absence of HGF, e.g., it increases c-Met tyrosine phosphorylation, and then the antibody is a mimic antibody. If the antibody cannot cause c-Met activation in the absence of HGF but is able to amplify the amount of c-Met activation, then the antibody is an amplifying antibody.

Inhibition of c-Met Tyrosine Phosphorylation, c-Met Levels, and Tumor Cell Growth *in vivo* by c-Met Antibodies

[00124] Another embodiment of the invention provides a c-Met antibody that inhibits c-Met tyrosine phosphorylation and receptor levels *in vivo*. In one embodiment, administration of c-Met antibody to an animal causes a reduction in c-Met phosphotyrosine signal in c-Met-expressing tumors. In a preferred embodiment, the c-Met antibody causes a reduction in phosphotyrosine signal by at least 20%. In a more preferred embodiment, the c-Met antibody causes a decrease in phosphotyrosine signal by at least 50%, more preferably 60%. In an even more preferred embodiment, the antibody causes a decrease in phosphotyrosine signal of at least 70%, more preferably 80%, even more preferably 90%. In a preferred embodiment, the antibody is administered approximately 24 hours before the levels of tyrosine phosphorylation are measured.

[00125] The levels of tyrosine phosphorylation may be measured by any method known in the art, such as those described *infra*. See, e.g., Example 5 and Figures 4 & 6. In a preferred embodiment, the antibody is selected from PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-

A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, and PGIA-05-A1, or comprises a heavy chain, light chain or antigen-binding portion thereof.

[00126] In another embodiment, administration of c-Met antibody to an animal causes a reduction in c-Met levels in c-Met-expressing tumors. In a preferred embodiment, the c-Met antibody causes a reduction in receptor levels by at least 20% compared to an untreated animal. In a more preferred embodiment, the c-Met antibody causes a decrease in receptor levels to at least 60%, more preferably 50% of the receptor levels in an untreated animal. In an even more preferred embodiment, the antibody causes a decrease in receptor levels to at least 40%, more preferably 30%. In a preferred embodiment, the antibody is administered approximately 24 hours before the c-Met levels are measured. The c-Met levels may be measured by any method known in the art, such as those described *infra*. In a preferred embodiment, the antibody is selected from PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, and PGIA-05-A1 or comprises a heavy chain, light chain or antigen-binding portion thereof.

[00127] In another embodiment, a c-Met antibody inhibits tumor cell growth *in vivo*. The tumor cell may be derived from any cell type including, without limitation, epidermal, epithelial, endothelial, leukemia, sarcoma, multiple myeloma, or mesodermal cells. Examples of common tumor cell lines for use in xenograft tumor studies include A549 (non-small cell lung carcinoma) cells, DU-145 cells, HCT-116 cells, MCF-7 cells, Colo 205 cells, 3T3/c-Met cells, 184B5 cells, NCI H441 cells, HEP G2 cells, MDA MB 231 cells, HT-29 cells, MDA-MB-435 cells, GTL-16 cells, BxPC3 cells, S114 cells, MDCK cells, A549 cells, U0118 MG cells, B16 cells, U-87 MG cells, and A431 cells. In a preferred embodiment, the antibody inhibits tumor cell

growth as compared to the growth of the tumor in an untreated animal. In a more preferred embodiment, the antibody inhibits tumor cell growth by 50%. In an even more preferred embodiment, the antibody inhibits tumor cell growth by 60%, 65%, 70%, or 75%. In one embodiment, the inhibition of tumor cell growth is measured at least 7 days after the animals have started treatment with the antibody. In a more preferred embodiment, the inhibition of tumor cell growth is measured at least 14 days after the animals have started treatment with the antibody. In another preferred embodiment, another antineoplastic agent is administered to the animal with the c-Met antibody. In a preferred embodiment, the antineoplastic agent is able to further inhibit tumor cell growth. In an even more preferred embodiment, the antineoplastic agent is Adriamycin, taxol, tamoxifen, 5-fluorodeoxyuridine (5-FU) or CP-358,774. In a preferred embodiment, the co-administration of an antineoplastic agent and the c-Met antibody inhibits tumor cell growth by at least 50%, more preferably 60%, 65%, 70% or 75%, more preferably 80%, 85% or 90% after a period of 22-24 days.

Induction of Apoptosis by c-Met Antibodies

[00128] Another aspect of the invention provides a c-Met antibody that induces cell death. In one embodiment, the antibody causes apoptosis. The antibody may induce apoptosis either *in vivo* or *in vitro*. In general, tumor cells are more sensitive to apoptosis than normal cells, such that administration of a c-Met antibody causes apoptosis of a tumor cell preferentially to that of a normal cell. In another embodiment, the administration of a c-Met antibody effects the activation of a kinase Akt, which is involved in the phosphatidyl inositol (PI) kinase pathway.

[00129] The PI kinase pathway, in turn, is involved in the cell proliferation and prevention of apoptosis. Thus, inhibition of Akt can cause apoptosis. In a more preferred embodiment, the antibody is administered *in vivo* to cause apoptosis of a HGF expressing cell. In a preferred embodiment, the antibody is selected from PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-

A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, and PGIA-05-A1, or comprises a heavy chain, light chain, or antigen-binding portion thereof.

Methods of Producing Antibodies and Antibody-Producing Cell Lines

Immunization

[00130] In one embodiment of the instant invention, human antibodies are produced by immunizing a non-human animal comprising some or the entire human immunoglobulin locus with a c-Met antigen. In a preferred embodiment, the non-human animal is a XENOMOUSE™, which is an engineered mouse strain that comprises large fragments of the human immunoglobulin loci and is deficient in mouse antibody production. See, e.g. Green et al. *Nature Genetics* 7: 13-21 (1994) and United States Patents 5,916,771, 5,939,598, 5,985,615, 5,998,209, 6,075,181, 6,091,001, 6,114, 598 and 6,130,364. See also WO 91/10741, published July 25, 1991, WO 94/02602, published February 3, 1994, WO 96/34096 and WO 96/33735, both published October 31, 1996, WO 98/16654, published April 23, 1998, WO 98/24893, published June 11, 1998, WO 98/50433, published November 12, 1998, WO 99/45031, published September 10, 1999, WO 99/53049, published October 21, 1999, WO 00/09560, published February 24, 2000 and WO 00/037504, published June 29, 2000. The XENOMOUSE™ produces an adult-like human repertoire of fully human antibodies, and generates antigen specific human Mabs. A second generation XENOMOUSE™ contains approximately 80% of the human antibody repertoire through introduction of megabase sized, germline configuration YAC fragments of the human heavy chain loci and κ light chain loci. See Mendez et al. *Nature Genetics* 15:146-156 (1997), Green and Jakobovits *J. Exp. Med.* 188:483-495 (1998), the disclosures of which are hereby incorporated by reference.

[00131] The invention also provides a method for making c-Met antibodies from non-human, non-mouse animals by immunizing non-human transgenic animals that comprise human immunoglobulin loci. One may produce such animals using the methods described immediately above. The methods disclosed in these patents may be modified as described in United States Patent 5,994,619. In a preferred embodiment, the non-human animals may be rats, sheep, pigs, goats, cattle, or horses. In another embodiment, the non-human animal comprising human immunoglobulin gene loci are animals that have a "minilocus" of human immunoglobulins. In the minilocus approach, an exogenous Ig locus is mimicked through the inclusion of individual genes from the Ig locus. Thus, one or more V_H genes, one or more D_H genes, one or more J_H genes, a mu constant region, and a second constant region (preferably a gamma constant region) are formed into a construct for insertion into an animal. This approach is described, *inter alia*, in U.S. Patent No. 5,545,807, 5,545,806, 5,625,825, 5,625,126, 5,633,425, 5,661,016, 5,770,429, 5,789, 650, 5,814,318, 5,591,669, 5,612,205, 5,721,367, 5,789,215, and 5,643,763, hereby incorporated by reference.

[00132] An advantage of the minilocus approach is the rapidity with which constructs including portions of the Ig locus can be generated and introduced into animals. However, a potential disadvantage of the minilocus approach is that there may not be sufficient immunoglobulin diversity to support full B-cell development, such that there may be lower antibody production.

[00133] In order to produce a human c-Met antibody, a non-human animal comprising some or all of the human immunoglobulin loci is immunized with a c-Met antigen and the antibody or the antibody-producing cell is isolated from the animal. The c-Met antigen may be isolated and/or purified c-Met and is preferably a human c-Met. In another embodiment, the c-Met antigen is a fragment of c-Met, preferably the extracellular domain of c-Met. In another embodiment, the c-Met antigen is a fragment that comprises at least one epitope of c-Met. In another embodiment, the c-Met antigen is a cell that expresses c-Met on its cell surface, preferably a cell that overexpresses c-Met on its cell surface.

[00134] Immunization of animals may be done by any method known in the art. See, e.g., Harlow and Lane, *Antibodies: A Laboratory Manual*, New York: Cold Spring Harbor Press, 1990. Methods for immunizing non-human animals such as mice, rats, sheep, goats, pigs, cattle and horses are well known in the art. See, e.g.,

Harlow, Lane supra, and United States Patent 5,994,619. In a preferred embodiment, the c-Met antigen is administered with an adjuvant to stimulate the immune response.

[00135] Such adjuvants include complete or incomplete Freund's adjuvant, RIBI (muramyl dipeptides), or ISCOM (immunostimulating complexes). Such adjuvants may protect the polypeptide from rapid dispersal by sequestering it in a local deposit, or they may contain substances that stimulate the host to secrete factors that are chemotactic for macrophages and other components of the immune system. Preferably, if a polypeptide is being administered, the immunization schedule will involve two or more administrations of the polypeptide, spread out over several weeks.

Production of Antibodies and Antibody-Producing Cell Lines

[00136] After immunization of an animal with a c-Met antigen, antibodies and/or antibody-producing cells may be obtained from the animal. A c-Met antibody-containing serum is obtained from the animal by bleeding or sacrificing the animal. The serum may be used as it is obtained from the animal, an immunoglobulin fraction may be obtained from the serum, or the c-Met antibodies may be purified from the serum. Serum or immunoglobulins obtained in this manner are polyclonal, which are disadvantageous because the amount of antibodies that can be obtained is limited and the polyclonal antibody has a heterogeneous array of properties. In another embodiment, antibody-producing immortalized hybridomas may be prepared from the immunized animal. After immunization, the animal is sacrificed and the splenic B cells are fused to immortalized myeloma cells as is well known in the art. See, e.g., Harlow and Lane, *supra*. In a preferred embodiment, the myeloma cells do not secrete immunoglobulin polypeptides (a non-secretory cell line). After fusion and antibiotic selection, the hybridomas are screened using c-Met, a portion thereof, or a cell expressing c-Met. In a preferred embodiment, the initial screening is performed using an enzyme-linked immunoassay (ELISA) or a radioimmunoassay (RIA), preferably an ELISA. An example of ELISA screening is provided in WO 00/37504, herein incorporated by reference.

[00137] In another embodiment, antibody-producing cells may be prepared from a human who has an autoimmune disorder and who expresses c-Met antibodies. Cells

expressing the c-Met antibodies may be isolated by isolating white blood cells and subjecting them to fluorescence activated cell sorting (FACS) or by panning on plates coated with c-Met or a portion thereof. These cells may be fused with a human non-secretory myeloma to produce human hybridomas expressing human c-Met antibodies. In general, this is a less preferred embodiment because it is likely that the c-Met antibodies will have a low affinity for c-Met.

[00138] C-Met antibody-producing hybridomas are selected, cloned and further screened for desirable characteristics, including robust hybridoma growth, high antibody production and desirable antibody characteristics, as discussed further below. Hybridomas may be cultured and expanded *in vivo* in syngeneic animals, in animals that lack an immune system, e.g., nude mice, or in cell culture *in vitro*.

[00139] Methods of selecting, cloning and expanding hybridomas are well known to those of ordinary skill in the art.

[00140] Preferably, the immunized animal is a non-human animal that expresses human immunoglobulin genes and the splenic B cells are fused to a myeloma derived from the same species as the non-human animal. More preferably, the immunized animal is a XENOMOUSE™ and the myeloma cell line is a non-secretory mouse myeloma, such as the myeloma cell line is NSO-bcl-2.

[00141] In one aspect, the invention provides hybridomas are produced that produce human c-Met antibodies. In a preferred embodiment, the hybridomas are mouse hybridomas, as described above. In another preferred embodiment, the hybridomas are produced in a non-human, non-mouse species such as rats, sheep, pigs, goats, cattle, or horses. In another embodiment, the hybridomas are human hybridomas, in which a human non-secretory myeloma is fused with a human cell expressing a c-Met antibody.

Nucleic Acids, Vectors, Host Cells, and Recombinant Methods of Making Antibodies

Nucleic Acids

[00142] Nucleic acid molecules encoding c-Met antibodies of the invention are provided. In one embodiment, the nucleic acid molecule encodes a heavy and/or light chain of a c-Met immunoglobulin. In a preferred embodiment, a single nucleic acid

molecule encodes a heavy chain of a c-Met immunoglobulin and another nucleic acid molecule encodes the light chain of a c-Met immunoglobulin. In a more preferred embodiment, the encoded immunoglobulin is a human immunoglobulin, preferably a human IgG. The encoded light chain may be a λ chain or a κ chain, preferably a λ chain.

[00143] The nucleic acid molecule encoding the variable region of the light chain may be derived from the A30, A27, or O12 Vκ gene. In another preferred embodiment, the nucleic acid molecule encoding the light chain comprises the joining region derived from Jκ1, Jκ2, or Jκ4. In an even more preferred embodiment, the nucleic acid molecule encoding the light chain contains no more than ten amino acid changes from the germline, preferably no more than six amino acid changes, and even more preferably no more than three amino acid changes.

[00144] The invention provides a nucleic acid molecule that encodes a variable region of the light chain (VL) containing at least three amino acid changes compared to the germline sequence, wherein the amino acid changes are identical to the amino acid changes from the germline sequence from the VL of one of the antibodies PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, and PGIA-05-A1. The invention also provides a nucleic acid molecule comprising a nucleic acid sequence that encodes the amino acid sequence of the variable region of the light chain of PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-

A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, or PGIA-05-A1. The invention also provides a nucleic acid molecule comprising a nucleic acid sequence that encodes the amino acid sequence of one or more of the CDRs of any one of the light chains of PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, or PGIA-05-A1. In a preferred embodiment, the nucleic acid molecule comprises a nucleic acid sequence that encodes the amino acid sequence of all of the CDRs of any one of the light chains of PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, or PGIA-05-A1. In another embodiment, the nucleic acid molecule comprises a nucleic acid sequence that encodes the VL amino acid sequence of one of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ

ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, or SEQ ID NO:60 or comprises a nucleic acid sequence of one of SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, or SEQ ID NO:120 or a fragment thereof.

[00145] In another preferred embodiment, the nucleic acid molecule comprises a nucleic acid sequence that encodes the amino acid sequence of one or more of the CDRs of any one of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID

NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, and SEQ ID NO:60 or comprises a nucleic acid sequence of one or more of the CDRs of any one of SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, or SEQ ID NO:120. In a more preferred embodiment, the nucleic acid molecule comprises a nucleic acid sequence that encodes the amino acid sequence of all of the CDRs of any one of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, or

SEQ ID NO:60 or comprises a nucleic acid sequence of all the CDRs of any one of SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, or SEQ ID NO:120. The invention also provides a nucleic acid molecules that encodes an amino acid sequence of a VL that has an amino acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a VL described above, particularly to a VL that comprises an amino acid sequence of one of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, or SEQ ID NO:60. The invention also provides a nucleic acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleic acid sequence of one of SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID

NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, or SEQ ID NO:120 or a fragment thereof. In another embodiment, the invention provides a nucleic acid molecule encoding a VL that hybridizes under highly stringent conditions to a nucleic acid molecule encoding a VL as described above, particularly a nucleic acid molecule that comprises a nucleic acid sequence encoding a VL amino acid sequence of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, and SEQ ID NO:60. The invention also provides a nucleic acid sequence encoding an VL that hybridizes under highly stringent conditions to a nucleic acid molecule comprising a nucleic acid sequence of one of SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83,

SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, and SEQ ID NO:120 or a nucleic acid sequence that would hybridize except for the degeneracy of the genetic code.

[00146] The invention also provides a nucleic acid molecule encoding the variable region of the heavy chain (VH) is derived from the DP-35, DP-47, DP-71, or VIV-4/4.35 VH gene. In another embodiment, the nucleic acid molecule encoding the VH comprises the joining region derived from JH6 or JH5. In another preferred embodiment, the D segment is derived from 3-3, 6-19 or 4-17. In an even more preferred embodiment, the nucleic acid molecule encoding the VH contains no more than ten amino acid changes from the germline gene, preferably no more than six amino acid changes, and even more preferably no more than three amino acid changes. In a highly preferred embodiment, the nucleic acid molecule encoding the VH contains at least one amino acid change compared to the germline sequence, wherein the amino acid change is identical to the amino acid change from the germline sequence from the heavy chain of one of the antibodies PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, or PGIA-05-A1. In an even more preferred embodiment, the VH contains at least three amino acid changes compared to the germline sequences, wherein the changes are identical

to those changes from the germline sequence from the VH of one of the antibodies PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, or PGIA-05-A1.

[00147] In one embodiment, the nucleic acid molecule comprises a nucleic acid sequence that encodes the amino acid sequence of the VH of PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, and PGIA-05-A1 or a fragment of any one thereof. In a preferred embodiment, the nucleic acid molecule comprises a nucleic acid sequence that encodes the amino acid sequence of PGIA-01-A8, PGIA-03-A9, PGIA-03-A11, PGIA-03-B2, PGIA-04-A5, PGIA-04-A8, and PGIA-05-A1 or a fragment of any one thereof. In a preferred embodiment, the nucleic acid molecule comprises a nucleic acid sequence that encodes the amino acid sequence of PGIA-03-A9, PGIA-04-A5, and PGIA-04-A8 or a fragment of any one thereof. Table 1 shows the amino acid sequences of the scFvs PGIA-01-A1 through PGIA-05-A1 above.

[00148] In another embodiment, the nucleic acid molecule comprises a nucleic acid sequence that encodes the amino acid sequence of one or more of the CDRs of the heavy chain of PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, or PGIA-05-A1. In a preferred embodiment, the nucleic acid molecule comprises a nucleic acid sequence that encodes the amino acid sequences of all of the CDRs of the heavy chain of PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, or PGIA-05-A1. In another preferred embodiment, the nucleic acid molecule comprises a nucleic acid sequence that encodes the VH amino acid sequence of one of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID

NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, or SEQ ID NO:60 or that comprises a nucleic acid sequence of one of SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, or SEQ ID NO:120. In another preferred embodiment, the nucleic acid molecule comprises a nucleic acid sequence that encodes the amino acid sequence of one or more of the CDRs of any one of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, or SEQ ID NO:60 or comprises a nucleic acid sequence of one or more of the

CDRs of any one of SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, and SEQ ID NO:120. In a preferred embodiment, the nucleic acid molecule comprises a nucleic acid sequence that encodes the amino acid sequences of all of the CDRs of any one SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, and SEQ ID NO:60 or comprises a nucleic acid sequence of all of the CDRs of any one of SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID

NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, and SEQ ID NO:120.

[00149] In another embodiment, the nucleic acid molecule encodes an amino acid sequence of a VH that is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to one of the amino acid sequences encoding a VH as described immediately above, particularly to a VH that comprises an amino acid sequence of one of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, or SEQ ID NO:60. The invention also provides a nucleic acid sequence that is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleic acid sequence of one of SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100,

SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, or SEQ ID NO:120. In another embodiment, the nucleic acid molecule encoding a VH is one that hybridizes under highly stringent conditions to a nucleic acid sequence encoding a VH as described above, particularly to a VH that comprises an amino acid sequence of one of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, or SEQ ID NO:60. The invention also provides a nucleic acid sequence encoding a VH that hybridizes under highly stringent conditions to a nucleic acid molecule comprising a nucleic acid sequence of one of SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID

NO:117, SEQ ID NO:118, SEQ ID NO:119, and SEQ ID NO:120 or a nucleic acid sequence that would hybridize except for the degeneracy of the genetic code.

[00150] The nucleic acid molecule encoding either or both of the entire heavy and light chains of an c-Met antibody or the variable regions thereof may be obtained from any source that produces an c-Met antibody. Methods of isolating mRNA encoding an antibody are well known in the art. See, e.g., Sambrook et al. The mRNA may be used to produce cDNA for use in the polymerase chain reaction (PCR) or cDNA cloning of antibody genes. In one embodiment of the invention, the nucleic acid molecules may be obtained from a hybridoma that expresses an c-Met antibody, as described above, preferably a hybridoma that has as one of its fusion partners a transgenic animal cell that expresses human immunoglobulin genes, such as a XENOMOUSE™, non-human mouse transgenic animal or a nonhuman, non-mouse transgenic animal. In another embodiment, the hybridoma is derived from a non-human, non-transgenic animal, which may be used, e.g., for humanized antibodies.

[00151] A nucleic acid molecule encoding the entire heavy chain of a c-Met antibody may be constructed by fusing a nucleic acid molecule encoding the variable domain of a heavy chain or an antigen-binding domain thereof with a constant domain of a heavy chain. Similarly, a nucleic acid molecule encoding the light chain of a c-Met antibody may be constructed by fusing a nucleic acid molecule encoding the variable domain of a light chain or an antigen-binding domain thereof with a constant domain of a light chain. The nucleic acid molecules encoding the VH and VL chain may be converted to full-length antibody genes by inserting them into expression vectors already encoding heavy chain constant and light chain constant regions, respectively, such that the VH segment is operatively linked to the heavy chain constant region (CH) segment(s) within the vector and the VL segment is operatively linked to the light chain constant region (CL) segment within the vector.

[00152] Alternatively, the nucleic acid molecules encoding the VH or VL chains are converted into full-length antibody genes by linking, e.g., ligating the nucleic acid molecule encoding a VH chain to a nucleic acid molecule encoding a CH chain using standard molecular biological techniques. The same may be achieved using nucleic acid molecules encoding VL and CL chains. The sequences of human heavy and light chain constant region genes are known in the art. See, e.g., Kabat et al., *Sequences of Proteins of Immunological Interest*, 5th Ed., NIH Publ. No. 91-3242, 1991. Nucleic

acid molecules encoding the full-length heavy and/or light chains may then be expressed from a cell into which they have been introduced and the c-Met antibody isolated.

[00153] In a preferred embodiment, the nucleic acid encoding the variable region of the heavy chain encodes the amino acid sequence of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, or SEQ ID NO:60, and the nucleic acid molecule encoding the variable region of the light chains encodes the amino acid sequence of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, and SEQ ID NO:60.

[00154] In another embodiment, a nucleic acid molecule encoding either the heavy chain of an c-Met antibody or an antigen-binding domain thereof, or the light chain of an c-Met antibody or an antigen-binding domain thereof may be isolated from a non-

human, non-mouse animal that expresses human immunoglobulin genes and has been immunized with an c-Met antigen. In other embodiment, the nucleic acid molecule may be isolated from a c-Met antibody-producing cell derived from a non-transgenic animal or from a human patient who produces c-Met antibodies. Methods of isolating mRNA from the c-Met antibody producing cells may be isolated by standard techniques, cloned and/or amplified using PCR and library construction techniques, and screened using standard protocols to obtain nucleic acid molecules encoding c-Met heavy and light chains.

[00155] The nucleic acid molecules may be used to recombinantly express large quantities of c-Met antibodies, as described below. The nucleic acid molecules may also be used to produce chimeric antibodies, single chain antibodies, immunoadhesins, diabodies, mutated antibodies and antibody derivatives, as described further below. If the nucleic acid molecules are derived from a non-human, non-transgenic animal, the nucleic acid molecules may be used for antibody humanization, also as described below.

[00156] In another embodiment, the nucleic acid molecules of the invention may be used as probes or PCR primers for specific antibody sequences. For instance, a nucleic acid molecule probe may be used in diagnostic methods or a nucleic acid molecule PCR primer may be used to amplify regions of DNA that could be used, *inter alia*, to isolate nucleic acid sequences for use in producing variable domains of c-Met antibodies. In a preferred embodiment, the nucleic acid molecules are oligonucleotides. In a more preferred embodiment, the oligonucleotides are from highly variable regions of the heavy and light chains of the antibody of interest. In an even more preferred embodiment, the oligonucleotides encode all or a part of one or more of the CDRs.

Vectors

[00157] The invention provides vectors comprising the nucleic acid molecules of the invention that encode the heavy chain or the antigen-binding portion thereof. The invention also provides vectors comprising the nucleic acid molecules of the invention that encode the light chain or antigen-binding portion thereof. The invention

also provides vectors comprising nucleic acid molecules encoding fusion proteins, modified antibodies, antibody fragments, and probes thereof.

[00158] To express the antibodies, or antibody portions of the invention, DNAs encoding partial or full-length light and heavy chains, obtained as described above, are inserted into expression vectors such that the genes are operatively linked to transcriptional and translational control sequences. Expression vectors include plasmids, retroviruses, cosmids, YACs, EBV derived episomes, and the like. The antibody gene is ligated into a vector such that transcriptional and translational control sequences within the vector serve their intended function of regulating the transcription and translation of the antibody gene. The expression vector and expression control sequences are chosen to be compatible with the expression host cell used. The antibody light chain gene and the antibody heavy chain gene can be inserted into separate vector. In a preferred embodiment, both genes are inserted into the same expression vector. The antibody genes are inserted into the expression vector by standard methods (e.g., ligation of complementary restriction sites on the antibody gene fragment and vector, or blunt end ligation if no restriction sites are present). A convenient vector is one that encodes a functionally complete human CH or CL immunoglobulin sequence, with appropriate restriction sites engineered so that any VH or VL sequence can be easily inserted and expressed, as described above.

[00159] In such vectors, splicing usually occurs between the splice donor site in the inserted J region and the splice acceptor site preceding the human C region, and also at the splice regions that occur within the human CH exons. Polyadenylation and transcription termination occur at native chromosomal sites downstream of the coding 10 regions. The recombinant expression vector can also encode a signal peptide that facilitates secretion of the antibody chain from a host cell. The antibody chain gene may be cloned into the vector such that the signal peptide is linked inframe to the amino terminus of the antibody chain gene. The signal peptide can be an immunoglobulin signal peptide or a heterologous signal peptide (i.e., a signal peptide from a non-immunoglobulin protein).

[00160] In addition to the antibody chain genes, the recombinant expression vectors of the invention carry regulatory sequences that control the expression of the antibody chain genes in a host cell. It will be appreciated by those skilled in the art that the design of the expression vector, including the selection of regulatory

sequences may depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, etc. Preferred regulatory sequences for mammalian host cell expression include viral elements that direct high levels of protein expression in mammalian cells, such as promoters and/or enhancers derived from retroviral LTRs, cytomegalovirus (CMV) (such as the CMV promoter/enhancer), Simian Virus 40 (SV40) (such as the SV40 promoter/enhancer), adenovirus, (e.g., the adenovirus major late promoter (AdMLP)), polyoma and strong mammalian promoters such as native immunoglobulin and actin promoters. For further description of viral regulatory elements, and sequences thereof, see e.g., U.S. Pat. No. 5,168,062 by Stinski, U.S. Pat. No. 4,510,245 by Bell et al. and U.S. Pat. No. 4,968,615 by Schaffner et al. In addition to the antibody chain genes and regulatory sequences, the recombinant expression vectors of the invention may carry additional sequences, such as sequences that regulate replication of the vector in host cells (e.g., origins of replication) and selectable marker genes. The selectable marker gene facilitates selection of host cells into which the vector has been introduced (see e.g., U.S. Pat. Nos. 4,399 216, 4,634,665, and 5,179,017, all by Axel et al.). For example, typically the selectable marker gene confers resistance to drugs, such as G418, hygromycin, or methotrexate, on a host cell into which the vector has been introduced. Preferred selectable marker genes include the dihydrofolate reductase (DHFR) gene (for use in dhfr- host cells with methotrexate selection/amplification) and the neo gene (for G418 selection).

Non-Hybridoma Host Cells and Methods of Recombinantly Producing Protein

[00161] Nucleic acid molecules encoding the heavy chain or an antigen binding portion thereof and/or the light chain or an antigen-binding portion thereof of a c-Met antibody, and vectors comprising these nucleic acid molecules, can be used for transformation of a suitable mammalian host cell. Transformation can be by any known method for introducing polynucleotides into a host cell. Methods for introduction of heterologous polynucleotides into mammalian cells are well known in the art and include dextran-mediated transfection, calcium phosphate precipitation, polybrene-mediated transfection, protoplast fusion, electroporation, and encapsulation of the polynucleotide(s) in liposomes, biolistic injection, and direct microinjection of

the DNA into nuclei. In addition, nucleic acid molecules may be introduced into mammalian cells by viral vectors. Methods of transforming cells are well known in the art. See, e.g., U.S. Patent Nos. 4,399,216, 4,912,040, 4,740,461, and 4,959,455 (which patents are hereby incorporated herein by reference).

[00162] Mammalian cell lines available as hosts for expression are well known in the art and include many immortalized cell lines available from the American Type Culture Collection (ATCC). These include, inter aria, Chinese hamster ovary (CHO) cells, NSO, SP2 cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (e.g., Hep G2), A549 cells, 3T3 cells, and a number of other cell lines. Mammalian host cells include human, mouse, rat, dog, monkey, pig, goat, bovine, horse, and hamster cells. Cell lines of particular preference are selected through determining which cell lines have high expression levels. Other cell lines that may be used are insect cell lines, such as Sf9 cells, amphibian cells, bacterial cells, plant cells, and fungal cells. When recombinant expression vectors encoding the heavy chain or antigen-binding portion thereof, the light chain and/or antigen-binding portion thereof are introduced into mammalian host cells, the antibodies are produced by culturing the host cells for a period of time sufficient to allow for expression of the antibody in the host cells or, more preferably, secretion of the antibody into the culture medium in which the host cells are grown. Antibodies can be recovered from the culture medium using standard protein purification methods.

[00163] Further, expression of antibodies of the invention (or other moieties therefrom) from production cell lines can be enhanced using a number of known techniques. For example, the glutamine synthetase gene expression system (the GS system) is a common approach for enhancing expression under certain conditions. The GS system is discussed in whole or part in connection with European Patent Nos. 0 216 846, 0 256 055, and 0 323 997 and European Patent Application No. 89303964.4.

[00164] It is likely that antibodies expressed by different cell lines or in transgenic animals will have different glycosylation from each other. However, all antibodies encoded by the nucleic acid molecules provided herein, or comprising the amino acid sequences provided herein are part of the instant invention, regardless of the glycosylation of the antibodies.

Transgenic Animals

[00165] The invention also provides transgenic non-human animals comprising one or more nucleic acid molecules of the invention that may be used to produce antibodies of the invention. Antibodies can be produced in and recovered from tissue or bodily fluids, such as milk, blood or urine, of goats, cows, horses, pigs, rats, mice, rabbits, hamsters or other mammals. See, e.g., U.S. Patent Nos. 5,827,690, 5,756, 687, 5,750,172, and 5,741,957. As described above, non-human transgenic animals that comprise human immunoglobulin loci can be produced by immunizing with c-Met or a portion thereof.

[00166] In another embodiment, non-human transgenic animals are produced by introducing one or more nucleic acid molecules of the invention into the animal by standard transgenic techniques. See Hogan, sierra. The transgenic cells used for making the transgenic animal can be embryonic stem cells or somatic cells. The transgenic non-human organisms can be chimeric, non-chimeric heterozygotes, and non-chimeric homozygotes. See, e.g., Hogan et al., *Manipulating the Mouse Embryo: A Laboratory Manual* 2 ed., Cold Spring Harbor Press (1999); Jackson et al., *Mouse Genetics and Transgenics: A Practical Approach*, Oxford University Press (2000); and Pinkert, *Transgenic Animal Technology: A Laboratory Handbook*, Academic Press (1999). In another embodiment, the transgenic non-human organisms may have a targeted disruption and replacement that encodes a heavy chain and/or a light chain of interest. In a preferred embodiment, the transgenic animals comprise and express nucleic acid molecules encoding heavy and light chains that bind specifically to c-Met, preferably human c-Met. In another embodiment, the transgenic animals comprise nucleic acid molecules encoding a modified antibody such as a single-chain antibody, a chimeric antibody or a humanized antibody. The c-Met antibodies may be made in any transgenic animal. In a preferred embodiment, the nonhuman animals are mice, rats, sheep, pigs, goats, cattle, or horses. The non-human transgenic animal expresses said encoded polypeptides in blood, milk, urine, saliva, tears, mucus, and other bodily fluids.

Phage Display Libraries

[00167] The invention provides a method for producing an c-Met antibody or antigen-binding portion thereof comprising the steps of synthesizing a library of human antibodies on phage, screening the library with a c-Met or a portion thereof, isolating phage that bind c-Met, and obtaining the antibody from the phage. One method to prepare the library of antibodies comprises the steps of immunizing a non-human host animal comprising a human immunoglobulin locus with c-Met or an antigenic portion thereof to create an immune response, extracting cells from the host animal the cells that are responsible for production of antibodies; isolating RNA from the extracted cells, reverse transcribing the RNA to produce cDNA, amplifying the cDNA using a primer, and inserting the cDNA into phage display vector such that antibodies are expressed on the phage. Recombinant c-Met antibodies of the invention may be obtained in this way.

[00168] Recombinant c-Met human antibodies of the invention in addition to the c-Met antibodies disclosed herein can be isolated by screening of a recombinant combinatorial antibody library, preferably a scFv phage display library, prepared using human VL and VH cDNAs prepared from mRNA derived from human lymphocytes. Methodologies for preparing and screening such libraries are known in the art. There are commercially available kits for generating phage display libraries (e.g., the Pharmacia Recombinant Phage Antibody System, catalog no. 27-9400-01; and the Stratagene SurZAP™ phage display kit, catalog no. 240612). There are also other methods and reagents that can be used in generating and screening antibody display libraries (see, e.g., Ladner et al. U.S. Pat. No. 5,223,409; Kang et al. PCT Publication No. WO 92/18619; Dower et al. PCT Publication No. WO 91/17271; Winter et al. PCT Publication No. WO 92/20791; Markland et al. PCT Publication No. WO 92/15679; Breitling et al. PCT Publication No. WO 93/01288; McCafferty et al. PCT Publication No. WO 92/01047; Garrard et al. PCT Publication No. WO 92/09690; Fuchs et al. (1991) *Bio/Technology* 9:1370-1372; Hay et al. (1992) *Hum. Antibody. Hybridomas* 3:81-85; Huse et al. (1989) Science 246:1275-1281; McCafferty et al., *Nature* (1990) 348:552-554; Griffiths et al. (1993) *EMBO J* 12:725-734; Hawkins et al. (1992) *J. Mol. Biol.* 226:889-896; Clackson et al. (1991) *Nature* 352:624-628; Gram et al. (1992) *Proc. Natl. Acad. Sci. USA* 89:3576-3580; Garrad et

al. (1991) *Bio/Technology* 9: 1373- 1377; Hoogenboom et al. (1991) *Nuc Acid Res* 19:4133-4137; and Barbas et al. (1991) *Proc. Natl. Acad. Sci. USA* 88:7978-7982.

[00169] In a preferred embodiment, to isolate human c-Met antibodies with the desired characteristics, a human c-Met antibody as described herein is first used to select human heavy and light chain sequences having similar binding activity toward c-Met, using the epitope imprinting methods described in Hoogenboom et al., PCT Publication No. WO 93/06213. The antibody libraries used in this method are preferably scFv libraries prepared and screened as described in McCafferty et al., PCT Publication No. WO 92/01047, McCafferty et al., *Nature* (1990) 348:552554; and Griffiths et al., (1993) *EMBO J* 12:725-734. The scFv antibody libraries preferably are screened using human c-Met as the antigen.

[00170] Once initial human VL and VH segments are selected, "mix and match" experiments, in which different pairs of the initially selected VL and VH segments are screened for c-Met binding, are performed to select preferred VL/VH pair combinations. Additionally, to further improve the quality of the antibody, the VL and VH segments of the preferred VL/VH pair(s) can be randomly mutated, preferably within the CDR3 region of VH and/or VL, in a process analogous to the *in vivo* somatic mutation process responsible for affinity maturation of antibodies during a natural immune response. This *in vitro* affinity maturation can be accomplished by amplifying VH and VL regions using PCR primers complimentary to the VH CDR3 or VL CDR3, respectively, which primers have been "spiked" with a random mixture of the four nucleotide bases at certain positions such that the resultant PCR products encode VH and VL segments into which random mutations have been introduced into the VH and/or VL CDR3 regions. These randomly mutated VH and VL segments can be rescreened for binding to c-Met.

[00171] Following screening and isolation of a c-Met antibody of the invention from a recombinant immunoglobulin display library, nucleic acid encoding the selected antibody can be recovered from the display package (e.g., from the phage genome) and subcloned into other expression vectors by standard recombinant DNA techniques. If desired, the nucleic acid can be further manipulated to create other antibody forms of the invention, as described below. To express a recombinant human antibody isolated by screening of a combinatorial library, the DNA encoding the

antibody is cloned into a recombinant expression vector and introduced into a mammalian host cells, as described above.

Class Switching

[00172] Another aspect of the instant invention is to provide a mechanism by which the class of a c-Met antibody may be switched with another. In one aspect of the invention, a nucleic acid molecule encoding VL or VH is isolated using methods well known in the art such that it does not include any nucleic acid sequences encoding CL or CH. The nucleic acid molecule encoding VL or VH are then operatively linked to a nucleic acid sequence encoding a CL or CH from a different class of immunoglobulin molecule. This may be achieved using a vector or nucleic acid molecule that comprises a CL or CH chain, as described above. For example, a c-Met antibody that was originally IgM may be class switched to an IgG. Further, the class switching may be used to convert one IgG subclass to another, e.g., from IgG1 to IgG2. A preferred method for producing an antibody of the invention comprising a desired isotypes comprises the steps of isolating a nucleic acid encoding the heavy chain of an c-Met antibody and a nucleic acid encoding the light chain of an c-Met antibody, obtaining the variable region of the heavy chain, ligating the variable region of the heavy chain with the constant domain of a heavy chain of the desired isotype, expressing the light chain and the ligated heavy chain in a cell, and collecting the c-Met antibody with the desired isotype.

Antibody Derivatives

[00173] One may use the nucleic acid molecules described above to generate antibody derivatives using techniques and methods known to one of ordinary skill in the art.

Humanized Antibodies

[00174] As was discussed above in connection with human antibody generation, there are advantages to producing antibodies with reduced immunogenicity. This can be accomplished to some extent using techniques of humanization and display

techniques using appropriate libraries. It will be appreciated that marine antibodies or antibodies from other species can be humanized or primatized using techniques well known in the art. See e.g. Winter and Harris *Immunol Today* 14:43-46 (1993) and Wright et al. *Crit. Reviews in Immunol.* 12125-168 (1992). The antibody of interest may be engineered by recombinant DNA techniques to substitute the CH1, CH2, CH3, hinge domains, and/or the framework domain with the corresponding human sequence (see WO 92/02190 and U.S. Patent Nos. 5,530,101, 5,585,089, 5,693,761, 5,693,792, 5,714,350, and 5, 777,085). In a preferred embodiment, the c-Met antibody can be humanized by substituting the CH1, CH2, CH3, hinge domains, and/or the framework domain with the corresponding human sequence while maintaining all of the CDRS of the heavy chain, the light chain or both the heavy and light chains.

Mutated Antibodies

[00175] In another embodiment, the nucleic acid molecules, vectors, and host cells may be used to make mutated c-Met antibodies. The antibodies may be mutated in the variable domains of the heavy and/or light chains to alter a binding property of the antibody. For example, a mutation may be made in one or more of the CDR regions to increase or decrease the K_d of the antibody for c-Met, to increase or decrease K_{off}, or to alter the binding specificity of the antibody. Techniques in site directed mutagenesis are well known in the art. See, e.g., Sambrook et al. and Ausubel et al., *supra*. In a preferred embodiment, mutations are made at an amino acid residue that is known to be changed compared to germline in a variable region of a c-Met antibody. In a more preferred embodiment, one or more mutations are made at an amino acid residue that is known to be changed compared to the germline in a variable region or CDR region of one of the c-Met antibodies PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5,

PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, and PGIA-05-A1. In another embodiment, one or more mutations are made at an amino acid residue that is known to be changed compared to the germline in a variable region or CDR region whose amino acid sequence is presented in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, and SEQ ID NO:60, or whose nucleic acid sequence is presented in SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, and SEQ ID NO:120.

[00176] In another embodiment, the nucleic acid molecules are mutated in one or more of the framework regions. A mutation may be made in a framework region or

constant domain to increase the half-life of the c-Met antibody. See, e.g., WO 00/09560, published February 24, 2000, herein incorporated by reference. In one embodiment, there may be one, three, or five point mutations and no more than ten point mutations. A mutation in a framework region or constant domain may also be made to alter the immunogenicity of the antibody, to provide a site for covalent or non-covalent binding to another molecule, or to alter such properties as complement fixation. Mutations may be made in each of the framework regions, the constant domain, and the variable regions in a single mutated antibody. Alternatively, mutations may be made in only one of the framework regions, the variable regions, or the constant domain in a single mutated antibody.

[00177] In one embodiment, there are no greater than ten amino acid changes in either the VH or VL regions of the mutated c-Met antibody compared to the c-Met antibody prior to mutation. In a more preferred embodiment, there are no more than five amino acid changes in either the VH or VL regions of the mutated c-Met antibody, more preferably no more than three amino acid changes. In another embodiment, there are no more than fifteen amino acid changes in the constant domains, more preferably, no more than ten amino acid changes, even more preferably, no more than five amino acid changes.

Modified Antibodies

[00178] In another embodiment, a fusion antibody or immunoadhesin may be made which comprises all or a portion of an anti- c-Met antibody linked to another polypeptide. In a preferred embodiment, only the variable regions of the c-Met antibody are linked to the polypeptide. In another preferred embodiment, the VH domain of an c-Met antibody are linked to a first polypeptide, while the VL domain of an c-Met antibody are linked to a second polypeptide that associates with the first polypeptide in a manner in which the VH and VL domains can interact with one another to form an antibody binding site. In another preferred embodiment, the VH domain is separated from the VL domain by a linker such that the VH and VL domains can interact with one another (see below under Single Chain Antibodies). The VH-linker-VL antibody is then linked to the polypeptide of interest. The fusion antibody is useful to directing a polypeptide to a c-Met expressing cell or tissue. The

polypeptide may be a therapeutic agent, such as a toxin, growth factor, or other regulatory protein, or may be a diagnostic agent, such as an enzyme that may be easily visualized, such as horseradish peroxidase. In addition, fusion antibodies can be created in which two (or more) single-chain antibodies are linked to one another. This is useful if one wants to create a divalent or polyvalent antibody on a single polypeptide chain, or if one wants to create a bispecific antibody.

[00179] To create a single chain antibody, (scFv) the VH- and VL-encoding DNA fragments are operatively linked to another fragment encoding a flexible linker, e.g., encoding the amino acid sequence $(Gly_4\text{-}Ser)_3$ (SEQ ID NO: 121), such that the VH and VL sequences can be expressed as a contiguous single-chain protein, with the VL and VH regions joined by the flexible linker (see e.g., Bird et al. (1988) *Science* 242:423-426; Huston et al. (1988) *Proc. Natl. Acad. Sci. USA* 85:5879-5883; McCafferty et al., *Nature* (1990) 348:552-554). The single chain antibody may be monovalent, if only a single VH and VL are used, bivalent, if two VH and VL are used, or polyvalent, if more than two VH and VL are used.

[00180] In another embodiment, other modified antibodies may be prepared using c-Met-encoding nucleic acid molecules. For instance, "Kappa bodies" (Ill et al., *Protein Eng* 10: 949-57 (1997)), "Minibodies" (Martin et al., *EMBO J* 13: 5303 9 (1994)), "Diabodies" (Holliger et al., *PNAS USA* 90: 6444-6448 (1993)), or "Janusins" (Traunecker et al., *EMBO J* 10: 3655-3659 (1991) and Traunecker et al. "Janusin: new molecular design for bispecific reagents" *Int J Cancer Suppl* 7:51-52 (1992)) may be prepared using standard molecular biological techniques following the teachings of the specification.

[00181] In another aspect, chimeric and bispecific antibodies can be generated. A chimeric antibody may be made that comprises CDRs and framework regions from different antibodies. In a preferred embodiment, the CDRs of the chimeric antibody comprises all of the CDRs of the variable region of a light chain or heavy chain of an c-Met antibody, while the framework regions are derived from one or more different antibodies. In a more preferred embodiment, the CDRs of the chimeric antibody comprise all of the CDRs of the variable regions of the light chain and the heavy chain of a c-Met antibody. The framework regions may be from another species and may, in a preferred embodiment, be humanized. Alternatively, the framework regions may be from another human antibody.

[00182] A bispecific antibody can be generated that binds specifically to c-Met through one binding domain and to a second molecule through a second binding domain. The bispecific antibody can be produced through recombinant molecular biological techniques, or may be physically conjugated together. In addition, a single chain antibody containing more than one VH and VL may be generated that binds specifically to c-Met and to another molecule. Such bispecific antibodies can be generated using techniques that are well known for example, in connection with (i) and (ii) see e.g. Fanger et al. *Immunol Methods* 4: 72-81 (1994) and Wright and Harris, *supra.* and in connection with (iii) see e.g. Traunecker et al. *Int. J. Cancer* (Suppl.) 7: 51-52 (1992). In a preferred embodiment, the bispecific antibody binds to c-Met and to another molecule expressed at high level on cancer or tumor cells. In a more preferred embodiment, the other molecule is RON, IGF-1R, erbB2 receptor, VEGF-2 or 3, CD20, or EGF-R.

[00183] In another embodiment, the modified antibodies described above are prepared using one or more of the variable regions or one or more CDR regions from one of the antibodies selected from PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, and PGIA-05-A1. In another embodiment, the modified antibodies are prepared using one or more of the variable regions or one or more CDR regions whose amino acid sequence is presented in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID

NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, and SEQ ID NO:60, or whose nucleic acid sequence is presented in SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, and SEQ ID NO:120.

Derivatized and Labeled Antibodies

[00184] An antibody or antibody portion of the invention can be derivatized or linked to another molecule (e.g., another peptide or protein). In general, the antibodies or portion thereof is derivatized such that the c-Met binding is not affected adversely by the derivatization or labeling. Accordingly, the antibodies and antibody portions of the invention are intended to include both intact and modified forms of the human c-Met antibodies described herein. For example, an antibody or antibody portion of the invention can be functionally linked (by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody (e.g., a bispecific antibody or a diabody), a detection agent, a cytotoxic agent, a pharmaceutical agent, and/or a protein or peptide that can mediate

associate of the antibody or antibody portion with another molecule (such as a streptavidin core region or a polyhistidine tag).

[00185] One type of derivatized antibody is produced by crosslinking two or more antibodies (of the same type or of different types, e.g., to create bispecific antibodies). Suitable crosslinkers include those that are heterobifunctional, having two distinctly reactive groups separated by an appropriate spacer (e.g., m-maleimidobenzoyl-N-hydroxysuccinimide ester) or homobifunctional (e.g., disuccinimidyl suberate). Such linkers are available from Pierce Chemical Company, Rockford, Ill.

[00186] Another type of derivatized antibody is a labeled antibody. Useful detection agents with which an antibody or antibody portion of the invention may be derivatized include fluorescent compounds, including fluorescein, fluorescein isothiocyanate, rhodamine, 5-dimethylamine-1-napthalenesulfonyl chloride, phycoerythrin, lanthanide phosphors and the like. An antibody may also be labeled with enzymes that are useful for detection, such as horseradish peroxidase, β-galactosidase, luciferase, alkaline phosphatase, glucose oxidase, and the like. When an antibody is labeled with a detectable enzyme, it is detected by adding additional reagents that the enzyme uses to produce a reaction product that can be discerned. For example, when the agent horseradish peroxidase is present, the addition of hydrogen peroxide and diaminobenzidine leads to a brown reaction product, which is detectable. An antibody may also be labeled with biotin, and detected through indirect measurement of avidin or streptavidin binding. An antibody may be labeled with a magnetic agent, such as gadolinium. An antibody may also be labeled with a predetermined polypeptide epitopes recognized by a secondary reporter (e.g., leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags). In some embodiments, labels are attached by spacer arms of various lengths to reduce potential steric hindrance.

[00187] A c-Met antibody may also be labeled with a radiolabeled amino acid. The radiolabel may be used for both diagnostic and therapeutic purposes. For instance, the radiolabel may be used to detect c-Met-expressing tumors by x-ray or other diagnostic techniques. Further, the radiolabel may be used therapeutically as a toxin for cancerous cells or tumors. Examples of labels for polypeptides include, but are not limited to, the following radioisotopes or radionuclides -- ^{3}H, ^{14}C, ^{15}N, ^{35}S, ^{90}Y ^{99}Tc ^{111}In, ^{125}I, and ^{131}I.

[00188] A c-Met antibody may also be derivatized with a chemical group such as polyethylene glycol (PEG), a methyl or ethyl group, or a carbohydrate group. These groups may be useful to improve the biological characteristics of the antibody, e.g., to increase serum half-life or to increase tissue binding.

Pharmaceutical Compositions and Kits

[00189] The invention also relates to a pharmaceutical composition for the treatment of a hyperproliferative disorder in a mammal, which comprises a therapeutically effective amount of a compound of the invention and a pharmaceutically acceptable carrier. In one embodiment, said pharmaceutical composition is for the treatment of cancer such as brain, lung, squamous cell, bladder, gastric, pancreatic, breast, head, neck, renal, kidney, ovarian, prostate, colorectal, esophageal, gynecological or thyroid cancer. In another embodiment, said pharmaceutical composition relates to non-cancerous hyperproliferative disorders such as, without limitation, restenosis after angioplasty and psoriasis. In another embodiment, the invention relates to pharmaceutical compositions for the treatment of a mammal that requires activation of c-Met, wherein the pharmaceutical composition comprises a therapeutically effective amount of an activating antibody of the invention and a pharmaceutically acceptable carrier. Pharmaceutical compositions comprising activating antibodies ma' be used to treat animals that lack sufficient HGF, or may be used to treat osteoporosis, frailty or disorders in which the mammal secretes too little active growth hormone or is unable to respond to growth hormone. The c-Met antibodies of the invention can be incorporated into pharmaceutical compositions suitable for administration to a subject. Typically, the pharmaceutical composition comprises an antibody of the invention and a pharmaceutically acceptable carrier. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Examples of pharmaceutically acceptable carriers include one or more of water, saline, phosphate buffered saline, dextrose, glycerol, ethanol and the like, as well as combinations thereof. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium

chloride in the composition. Pharmaceutically acceptable substances such as wetting or minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives or buffers, which enhance the shelf life or effectiveness of the antibody or antibody portion.

[00190] The compositions of this invention may be in a variety of forms. These include, for example, liquid, semi-solid, and solid dosage forms, such as liquid solutions (e.g., injectable and infusible solutions), dispersions or suspensions, tablets, pills, powders, liposomes and suppositories. The preferred form depends on the intended mode of administration and therapeutic application. Typical preferred compositions are in the form of injectable or infusible solutions, such as compositions similar to those used for passive immunization of humans with other antibodies. The preferred mode of administration is parenteral (e.g., intravenous, subcutaneous, intraperitoneal, intramuscular). In a preferred embodiment, the antibody is administered by intravenous infusion or injection. In another preferred embodiment, the antibody is administered by intramuscular or subcutaneous injection.

[00191] Therapeutic compositions typically must be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, dispersion, liposome, or other ordered structure suitable to high drug concentration. Sterile injectable solutions can be prepared by incorporating the c-Met antibody in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The proper fluidity of a solution can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prolonged absorption of injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, monostearate salts, and gelatin.

[00192] The antibodies of the present invention can be administered by a variety of methods known in the art, although for many therapeutic applications, the preferred route/mode of administration is intraperitoneal, subcutaneous, intramuscular, intravenous, or infusion. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results. In one embodiment, the antibodies of the present inventor can be administered as a single dose or may be administered as multiple doses.

[00193] In certain embodiments, the active compound may be prepared with a carrier that will protect the compound against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Many methods for the preparation of such formulations are patented or generally known to those skilled in the art. See, e.g., *Sustained and Controlled Release Drug Delivery Systems*, J. R. Robinson, ed., Marcel Dekker, Inc., New York, 1978.

[00194] In certain embodiments, the c-Met of the invention may be orally administered, for example, with an inert diluent or an assimilable edible carrier. The compound (and other ingredients, if desired) may also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, or incorporated directly into the subject's diet. For oral therapeutic administration, the compounds may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. To administer a compound of the invention by other than parenteral administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation.

[00195] Supplementary active compounds can also be incorporated into the compositions. In certain embodiments, a c-Met antibody of the invention is coformulated with and/or coadministered with one or more additional therapeutic agents, such as a chemotherapeutic agent, an antineoplastic agent, or an anti-tumor agent. For example, a c-Met antibody may be coformulated and/or coadministered with one or more additional therapeutic agents. These agents include, without limitation, antibodies that bind other targets (e.g., antibodies that bind one or more

growth factors or cytokines, their cell surface receptors or HGF), HGF binding proteins, antineoplastic agents, chemotherapeutic agents, antitumor agents, antisense oligonucleotides against c-Met or HGF, peptide analogues that block c-Met activation, soluble c-Met, and/or one or more chemical agents that inhibit HGF production or activity, which are known in the art, e.g., octreotide. For a pharmaceutical composition comprising an activating antibody, the c-Met antibody may be formulated with a factor that increases cell proliferation or prevents apoptosis. Such factors include growth factors such as HGF, and/or analogues of HGF that activate c-Met. Such combination therapies may require lower dosages of the c-Met antibody as well as the co-administered agents, thus avoiding possible toxicities or complications associated with the various monotherapies. In one embodiment, composition comprises the antibody and one or more additional therapeutic agent.

[00196] The pharmaceutical compositions of the invention may include a "therapeutically effective amount" or a "prophylactically effective amount" of an antibody or antibody portion of the invention. A "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount of the antibody or antibody portion may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antibody or antibody portion to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic detrimental effects of the antibody or antibody portion are outweighed by the therapeutically beneficial effects. A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. Typically, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease, the prophylactically effective amount will be less than the therapeutically effective amount.

[00197] Dosage regimens may be adjusted to provide the optimum desired response (e.g., a therapeutic or prophylactic response). For example, a single bolus may be administered, several divided doses may be administered over time, or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. Pharmaceutical composition comprising the antibody or comprising a combination therapy comprising the antibody and one or more additional therapeutic agents may be formulated for single or multiple doses. It is

especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active compound and the particular therapeutic or prophylactic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals. A particularly useful formulation is 5 mg/ml c-Met antibody in a buffer of 20 mM sodium citrate, pH 5.5, 140 mM NaCl, and 0.2 mg/ml polysorbate 80.

[00198] An exemplary, non-limiting range for a therapeutically or prophylactically effective amount of an antibody or antibody portion of the invention is 0.1-100 mg/kg, more preferably 0.5-50 mg/kg, more preferably 1-20 mg/kg, and even more preferably 1-10 mg/kg. It is to be noted that dosage values may vary with the type and severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that dosage ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. In one embodiment, the therapeutically or prophylactically effective amount of an antibody or antigen-binding portion thereof is administered along with one or more additional therapeutic agents.

[00199] Another aspect of the present invention provides kits comprising the c-Met antibodies and the pharmaceutical compositions comprising these antibodies. A kit may include, in addition to the antibody or pharmaceutical composition, diagnostic or therapeutic agents. A kit may also include instructions for use in a diagnostic or therapeutic method. In a preferred embodiment, the kit includes the antibody or a pharmaceutical composition thereof and a diagnostic agent that can be used in a method described below. In another preferred embodiment, the kit includes the antibody or a pharmaceutical composition thereof and one or more therapeutic agents,

such as an additional antineoplastic agent, anti-tumor agent, or chemotherapeutic agent, which can be used in a method described below.

[00200] This invention also relates to pharmaceutical compositions for inhibiting abnormal cell growth in a mammal which comprise an amount of a compound of the invention in combination with an amount of a chemotherapeutic agent, wherein the amounts of the compound, salt, solvate, or prodrug, and of the chemotherapeutic agent are together effective in inhibiting abnormal cell growth. Many chemotherapeutic agents are presently known in the art. In one embodiment, the chemotherapeutic agents is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, anti-survival agents, biological response modifiers, anti-hormones, e.g. anti-androgens, and anti angiogenesis agents.

[00201] Anti-angiogenic agents, such as MMP-2 (matrix-metalloproteinase 2) inhibitors, MMP-9 (matrix-metalloproteinase 9) inhibitors, and COX-II (cyclooxygenase II) inhibitors, can be used in conjunction with a compound of the invention. Examples of useful COX-II inhibitors include CELEBREX™ (celecoxib), BEXTRA™ (valdecoxib), and rofecoxib. Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 (published October 24, 1996), WO 96/27583 (published March 7, 1996), European Patent Application No. 97304971.1 (filed July 8, 1997), European Patent Application No. 99308617.2 (filed October 29, 1999), WO 98/07697 (published February 26, 1998), WO 98/03516 (published January 29, 1998), WO 98/34918 (published August 13, 1998), WO 98/34915 (published August 13, 1998), WO 98/33768 (published August 6, 1998), WO 98/30566 (published July 16, 1998), European Patent Publication 606,046 (published July 13, 1994), European Patent Publication 931,788 (published July 28, 1999), WO 90/05719 (published May 31, 1990), WO 99/52910 (published October 21, 1999), WO 99/52889 (published October 21, 1999), WO 99/29667 (published June 17, 1999), PCT International Application No. PCT/IB98/01113 (filed July 21, 1998), European Patent Application No. 99302232.1 (filed March 25, 1999), Great Britain patent application number 9912961.1 (filed June 3, 1999), United States Provisional Application No. 60/148,464 (filed August 12, 1999), United States Patent 5,863,949 (issued January 26, 1999), United States Patent 5,861,510 (issued January

19, 1999), and European Patent Publication 780,386 (published June 25, 1997), all of which are incorporated herein in their entireties by reference. Preferred MMP inhibitors are those that do not demonstrate arthralgia. More preferred, are those that selectively inhibit MMP-2 And/or MMP-9 relative to the other matrix-metalloproteinases (i.e. MMP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP- 10, MMP- 11, MMP- 12, and MMP-13). Some specific examples of MMP inhibitors useful in the present invention are AG-3340, RO 32-3555, RS 13-0830, and the compounds recited in the following list: 3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-cyclopentyl)-amino]-propionic acid; 3-exo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8-oxa bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide; (2R, 3R) 1-[4-(2-chloro-4 fluoro-benzyloxy)benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide; 4-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro pyran-4-carboxylic acid hydroxyamide; 3-[[4-(4-fluoro-phenoxy)benzenesulfonyl] (1-hydroxycarbamoyl-cyclobutyl)-amino]-propionic acid; 4[4-(4-chloro-phenoxy) benzenesulfonylamino]-tetrahydro-pyran-4-carboxylic acid hydroxyamide; (R) 3-[4 (4-chloro-phenoxy)-benzenesulfonylamino]tetrahydro-pyran-3-carboxylic acid hydroxyamide; (2R, 3R) 1-[4-(4-fluoro-2-methyl-benzyloxy)-benzenesulfonyl]-3 hydroxy-3-methyl-piperidine- 2-carboxylic acid hydroxyamide; 3-[[4-(4-fluoro phenoxy)-benzenesulfonyl] -(1-hydroxycarbamoyl-1-methyl-ethyl)-amino] -propionic acid; 3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(4-hydroxycarbamoyl-tetrahydro pyran-4- yl)-amino]-propionic acid; 3-exo-3-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-8-oxa-icyclo[3.2.1]octane-3-carboxylic acid hydroxyamide; 3-endo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8-oxaicyclo[3.2.1]octane-3 carboxylic acid hydroxyamide; and (R) 3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro-furan-3-carboxylic acid hydroxyamide; and pharmaceutically acceptable salts and solvates of said compounds.

[00202] A compound of the invention can also be used with signal transduction inhibitors, such as agents that can inhibit EGF-R (epidermal growth factor receptor) responses, such as EGF-R antibodies, EGF antibodies, and molecules that are EGF-R inhibitors; VEGF (vascular endothelial growth factor) inhibitors, such as VEGF receptors and molecules that can inhibit VEGF; and erbB2 receptor inhibitors, such as organic molecules or antibodies that bind to the erbB2 receptor, for example,

HERCEPTIN™ (Genentech, Inc.). EGF-R inhibitors are described in, for example in WO 95/19970 (published July 27, 1995), WO 98/14451 (published April 9, 1998), WO 98/02434 (published January 22, 1998), and United States Patent 5,747,498 (issued May 5, 1998), and such substances can be used in the present invention as described herein. EGFR-inhibiting agents include, but are not limited to, the monoclonal antibodies C225 and anti-EGFR 22Mab (ImClone Systems Incorporated), ABX-EGF (Abgenix/Cell Genesys), EMD-7200 (Merck KgaA), EMD-5590 (Merck KgaA), MDX-447/H-477 (Medarex Inc. and Merck KgaA), and the compounds ZD 1834, ZD-1838 and ZD-1839 (AstraZeneca), PKI-166 (Novartis), PKI-166/CGP 75166 (Novartis), PTK 787 (Novartis), CP 701 (Cephalon), leflunomide (Pharmacia/Sugen), CI-1033 (Warner Lambert Parke Davis), CI-1033/PD 183,805 (Warner Lambert Parke Davis), CL-387,785 (Wyeth-Ayerst), BBR-1611 (Boehringer Mannheim GmbH/Roche), Naamidine A (Bristol Myers Squibb), RC-3940-II (Pharmacia), BIBX-1382 (Boehringer Ingelheim), OLX-103 (Merck & Co.), VRCTC 310 (Ventech Research), EGF fusion toxin (Seragen Inc.), DAB-389 (Seragen/Ligand), ZM-252808 (Imperial Cancer Research Fund), RG-50864 (INSEAM), LFM-A12 (Parker Hughes Cancer Center), WHI-P97 (Parker Hughes Cancer Center), GW-282974 (Glaxo), KT-8391 (Kyowa Hakko) and EGF-R Vaccine (York Medical/Centro de Immunologia Molecular (CIM)). These and other EGF-R inhibiting agents can be used in the present invention.

[00203] VEGF inhibitors, for example SU-11248 (Sugen Inc.), SH-268 (Schering), and NX-1838 (NeXstar) can also be combined with the compound of the present invention. VEGF inhibitors are described in, for example in WO 99/24440 (published May 20, 1999), PCT International Application PCT/IB99/00797 (filed May 3, 1999), in WO 95/21613 (published August 17, 1995), WO 99/61422 (published December 2, 1999), United States Patent 5,834,504 (issued November 10, 1998), WO 98/50356 (published November 12, 1998), United States Patent 5,883,113 (issued March 16, 1999), United States Patent 5,886,020 (issued March 23, 1999), United States Patent 5,792,783 (issued August 11, 1998), WO 99/10349 (published March 4, 1999), WO 97/32856 (published September 12, 1997), WO 97/22596 (published June 26, 1997), WO 98/54093 (published December 3, 1998), WO 98/02438 (published January 22, 1998), WO 99/16755 (published April 8, 1999), and WO 98/02437 (published January 22, 1998), all of which are incorporated herein in their entireties by reference.

Other examples of some specific VEGF inhibitors useful in the present invention are IM862 (Cytran Inc.); anti-VEGF monoclonal antibody of Genentech, Inc.; and angiozyme, a synthetic ribozyme from Ribozyme and Chiron. These and other VEGF inhibitors can be used in the present invention as described herein.

[00204] ErbB2 receptor inhibitors, such as GW-282974 (Glaxo Wellcome plc), and the monoclonal antibodies AR-209 (Aronex Pharmaceuticals Inc.) and 2B-I (Chiron), can furthermore be combined with the compound of the invention, for example those indicated in WO 98/02434 (published January 22, 1998), WO 99/35146 (published July 15, 1999), WO 99/35132 (published July 15, 1999), WO 98/02437 (published January 22, 1998), WO 97/13760 (published April 17, 1997), WO 95/19970 (published July 27, 1995), United States Patent 5,587,458 (issued December 24, 1996), and United States Patent 5, 877,305 (issued March 2, 1999), which are all hereby incorporated herein in their entireties by reference. ErbB2 receptor inhibitors useful in the present invention are also described in United States Provisional Application No. 60/117,341, filed January 27, 1999, and in United States Provisional Application No. 60/117,346, filed January 27, 1999, both of which are incorporated in their entireties herein by reference. The erbB2 receptor inhibitor compounds and substance described in the aforementioned PCT applications, U.S. patents, and U.S. provisional applications, as well as other compounds and substances that inhibit the erbB2 receptor, can be used with the compound of the present invention in accordance with the present invention.

[00205] IGF-1 receptor inhibitors, such as the anti-IGF-1R antibodies of WO 02/053596 can be used in combination with the antibodies of the present invention.

[00206] Another component of the combination of the present invention is a cycloxygenase-2 selective inhibitor. The terms "cyclooxygenase-2 selective inhibitor", or "Cox-2 selective inhibitor", which can be used interchangeably herein, embrace compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1, and also include pharmaceutically acceptable salts of those compounds.

[00207] In practice, the selectivity of a Cox-2 inhibitor varies depending upon the condition under which the test is performed and on the inhibitors being tested. However, for the purposes of this specification, the selectivity of a Cox-2 inhibitor can be measured as a ratio of the *in vitro* or *in vivo* IC_{50} value for inhibition of Cox-1,

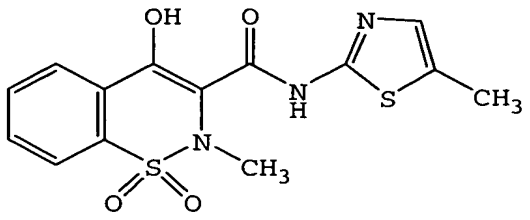
divided by the IC_{50} value for inhibition of Cox-2 (Cox-1 IC_{50}/Cox-2 IC_{50}). A Cox-2 selective inhibitor is any inhibitor for which the ratio of Cox-1 IC_{50} to Cox-2 IC_{50} is greater than 1. In preferred embodiments, this ratio is greater than 2, more preferably greater than 5, yet more preferably greater than 10, still more preferably greater than 50, and more preferably still greater than 100.

[00208] As used herein, the term "IC_{50}" refers to the concentration of a compound that is required to produce 50% inhibition of cyclooxygenase activity. Preferred cyclooxygenase-2 selective inhibitors of the present invention have a cyclooxygenase-2 IC_{50} of less than about 1 μM, more preferred of less than about 0.5 μM, and even more preferred of less than about 0.2 μM.

[00209] Preferred cycloxoygenase-2 selective inhibitors have a cyclooxygenase-1 IC_{50} of greater than about 1 μM, and more preferably of greater than 20 μM. Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

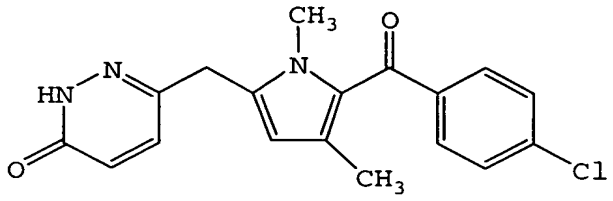
[00210] Also included within the scope of the present invention are compounds that act as prodrugs of cyclooxygenase-2-selective inhibitors. As used herein in reference to Cox-2 selective inhibitors, the term "prodrug" refers to a chemical compound that can be converted into an active Cox-2 selective inhibitor by metabolic or simple chemical processes within the body of the subject. One example of a prodrug for a Cox-2 selective inhibitor is parecoxib, which is a therapeutically effective prodrug of the tricyclic cyclooxygenase-2 selective inhibitor valdecoxib. An example of a preferred Cox-2 selective inhibitor prodrug is parecoxib sodium. A class of prodrugs of Cox-2 inhibitors is described in U.S. Patent No. 5,932,598.

[00211] The cyclooxygenase-2 selective inhibitor of the present invention can be, for example, the Cox-2 selective inhibitor meloxicam, Formula B-1 (CAS registry number 71125-38-7), or a pharmaceutically acceptable salt or prodrug thereof.



B-1

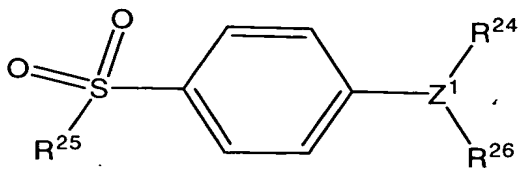
[00212] In another embodiment of the invention the cyclooxygenase-2 selective inhibitor can be the Cox-2 selective inhibitor RS 57067, 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, Formula B-2 (CAS registry number 179382-91-3), or a pharmaceutically acceptable salt or prodrug thereof.



B-2

[00213] In a another embodiment of the invention the cyclooxygenase-2 selective inhibitor is of the chromene/chroman structural class that is a substituted benzopyran or a substituted benzopyran analog, and even more preferably selected from the group consisting of substituted benzothiopyrans, dihydroquinolines, or dihydronaphthalenes. Benzopyrans that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include substituted benzopyran derivatives that are described in U.S. Patent No. 6,271,253. Other benzopyran Cox-2 selective inhibitors useful in the practice of the present invention are described in U.S. Patent Nos. 6,034,256 and 6,077,850.

[00214] In a further preferred embodiment of the invention the cyclooxygenase inhibitor can be selected from the class of tricyclic cyclooxygenase-2 selective inhibitors represented by the general structure of formula **I**:



I

wherein:

Z^1 is selected from the group consisting of partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

R^{24} is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R^{24} is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

R^{25} is selected from the group consisting of methyl or amino; and

R^{26} is selected from the group consisting of a radical selected from H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl;

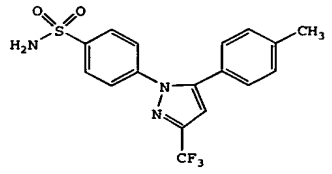
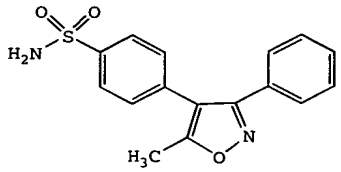
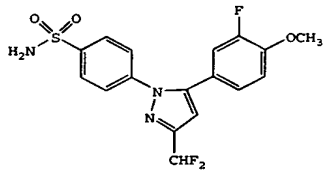
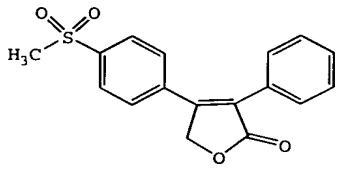
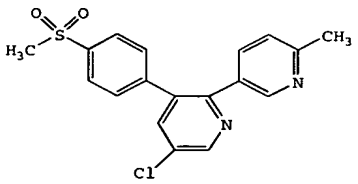
or a prodrug thereof.

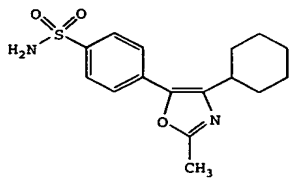
[00215] In a preferred embodiment of the invention the cyclooxygenase-2 selective inhibitor represented by the above Formula I is selected from the group of compounds, illustrated in Table 3, which includes celecoxib (B-3), valdecoxib (B-4), deracoxib (B-5), rofecoxib (B-6), etoricoxib (MK-663; B-7), JTE-522 (B-8), or a prodrug thereof.

[00216] Additional information about selected examples of the Cox-2 selective inhibitors discussed above can be found as follows: celecoxib (CAS RN 169590-42-5, C-2779, SC-58653, and in U.S. Patent No. 5,466,823); deracoxib (CAS RN 169590-41-4); rofecoxib (CAS RN 162011-90-7); compound B-24 (U.S. Patent No.

5,840,924); compound B-26 (WO 00/25779); and etoricoxib (CAS RN 202409-33-4, MK-663, SC-86218, and in WO 98/03484).

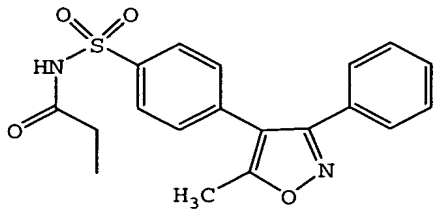
TABLE 3

Compound Number	Structural Formula
B-3	
B-4	
B-5	
B-6	
B-7	

Compound Number	Structural Formula
B-8	

[00217] In a more preferred embodiment of the invention, the Cox-2 selective inhibitor is selected from the group consisting of celecoxib, rofecoxib and etoricoxib.

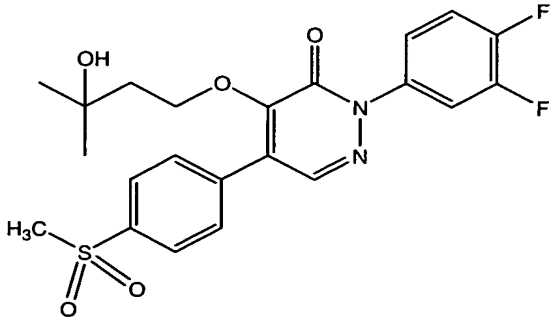
[00218] In a preferred embodiment of the invention, parecoxib (See, *e.g.* U.S. Patent No. 5,932,598), having the structure shown in B-9, which is a therapeutically effective prodrug of the tricyclic cyclooxygenase-2 selective inhibitor valdecoxib, B-4, (See, *e.g.*, U.S. Patent No. 5,633,272), may be advantageously employed as a source of a cyclooxygenase inhibitor.



B-9

A preferred form of parecoxib is sodium parecoxib.

[00219] In another embodiment of the invention, the compound ABT-963 having the formula B-10 that has been previously described in International Publication number WO 00/24719, is another tricyclic cyclooxygenase-2 selective inhibitor which may be advantageously employed.

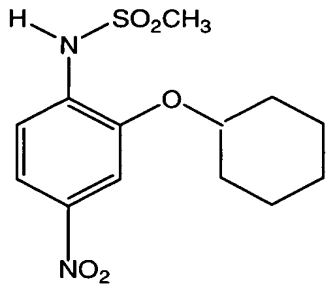


B-10

[00220] In a further embodiment of the invention, the cyclooxygenase inhibitor can be selected from the class of phenylacetic acid derivative cyclooxygenase-2 selective inhibitors described in WO 99/11605 WO 02/20090 is a compound that is referred to as COX-189 (also termed lumiracoxib), having CAS Reg. No. 220991-20-8.

[00221] Compounds that have a structure similar can serve as the Cox-2 selective inhibitor of the present invention, are described in U.S. Patent Nos. 6,310,099, 6,291,523, and 5,958,978.

[00222] Further information on the applications of the Cox-2 selective inhibitor N-(2-cyclohexyloxynitrophenyl) methane sulfonamide (NS-398, CAS RN 123653-11-2), having a structure as shown in formula B-11, have been described by, for example, Yoshimi, N. *et al.*, in *Japanese J. Cancer Res., 90(4):*406 - 412 (1999); Falgueyret, J.-P. *et al.*, in *Science Spectra,* available at: http://www.gbhap.com/Science-_Spectra/20-1-article.htm (06/06/2001); and Iwata, K. *et al.*, in *Jpn. J. Pharmacol., 75(2):*191 - 194 (1997).



B-11

[00223] An evaluation of the anti-inflammatory activity of the cyclooxygenase-2 selective inhibitor, RWJ 63556, in a canine model of inflammation, was described by Kirchner *et al.*, in *J Pharmacol Exp Ther 282*, 1094-1101 (1997).

[00224] Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include diarylmethylidenefuran derivatives that are described in U.S. Patent No. 6,180,651.

[00225] Particular materials that are included in this family of compounds, and which can serve as the cyclooxygenase-2 selective inhibitor in the present invention,

include N-(2-cyclohexyloxynitrophenyl)methane sulfonamide, and (E)-4-[(4-methylphenyl)(tetrahydro-2-oxo-3-furanylidene) methyl]benzenesulfonamide.

[00226] Cyclooxygenase-2 selective inhibitors that are useful in the present invention include darbufelone (Pfizer), CS-502 (Sankyo), LAS 34475 (Almirall Profesfarma), LAS 34555 (Almirall Profesfarma), S-33516 (Servier), SD 8381 (Pharmacia, described in U.S. Patent No. 6,034,256), BMS-347070 (Bristol Myers Squibb, described in U.S. Patent No. 6,180,651), MK-966 (Merck), L-783003 (Merck), T-614 (Toyama), D-1367 (Chiroscience), L-748731 (Merck), CT3 (Atlantic Pharmaceutical), CGP-28238 (Novartis), BF-389 (Biofor/Scherer), GR-253035 (Glaxo Wellcome), 6-dioxo-9H-purin-8-yl-cinnamic acid (Glaxo Wellcome), and S-2474 (Shionogi).

[00227] Information about S-33516, mentioned above, can be found in *Current Drugs Headline News*, at http://www.current-drugs.com/NEWS/Inflam1.htm, 10/04/2001, where it was reported that S-33516 is a tetrahydroisoinde derivative which has IC_{50} values of 0.1 and 0.001 mM against cyclooxygenase-1 and cyclooxygenase-2, respectively. In human whole blood, S-33516 was reported to have an ED_{50} = 0.39 mg/kg.

[00228] Compounds that may act as cyclooxygenase-2 selective inhibitors include multibinding compounds containing from 2 to 10 ligands covanlently attached to one or more linkers, as described in U.S. Patent No. 6,395,724. Compounds that may act as cyclooxygenase-2 inhibitors include conjugated linoleic acid that is described in U.S. Patent No. 6,077,868. Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include heterocyclic aromatic oxazole compounds that are described in U.S. Patents 5,994,381 and 6,362,209. Cox-2 selective inhibitors that are useful in the subject method and compositions can include compounds that are described in U.S. Patent Nos. 6,080,876 and 6,133,292. Materials that can serve as cyclooxygenase-2 selective inhibitors include pyridines that are described in U.S. Patent Nos. 6, 369,275, 6,127,545, 6,130,334, 6,204,387, 6,071,936, 6,001,843 and 6,040,450. Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include diarylbenzopyran derivatives that are described in U.S. Patent No. 6,340,694. Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include 1-(4-sulfamylaryl)-3-substituted-5-aryl-2-pyrazolines that are described in U.S. Patent No. 6,376,519.

[00229] Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include heterocycles that are described in U.S. Patent No. 6,153,787. Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include 2,3,5-trisubstituted pyridines that are described in U.S. Patent No. 6,046,217. Materials that can serve as the cyclooxygenase-2 selective inhibitor of the present invention include diaryl bicyclic heterocycles that are described in U.S. Patent No. 6,329,421. Compounds that may act as cyclooxygenase-2 inhibitors include salts of 5-amino or a substituted amino 1,2,3-triazole compound that are described in U.S. Patent No. 6,239,137.

[00230] Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include pyrazole derivatives that are described in U.S. Patent 6,136,831. Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include substituted derivatives of benzosulphonamides that are described in U.S. Patent 6,297,282. Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include bicycliccarbonyl indole compounds that are described in U.S. Patent No. 6,303,628. Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include benzimidazole compounds that are described in U.S. Patent No. 6,310,079. Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include indole compounds that are described in U.S. Patent No. 6,300,363. Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include aryl phenylhydrazides that are described in U.S. Patent No. 6,077,869. Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include 2-aryloxy, 4-aryl furan-2-ones that are described in U.S. Patent No. 6,140,515. Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include bisaryl compounds that are described in U.S. Patent No. 5,994,379. Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include 1,5-diarylpyrazoles that are described in U.S. Patent No. 6,028,202. Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include 2-substituted imidazoles that are described in U.S. Patent No. 6,040,320. Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include 1,3- and 2,3-diarylcycloalkano and cycloalkeno pyrazoles that are described in U.S. Patent No. 6,083,969. Materials that can serve as

a cyclooxygenase-2 selective inhibitor of the present invention include esters derived from indolealkanols and novel amides derived from indolealkylamides that are described in U.S. Patent No. 6,306,890. Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include pyridazinone compounds that are described in U.S. Patent No. 6,307,047. Materials that can serve as a cyclooxygenase-2 selective inhibitor of the present invention include benzosulphonamide derivatives that are described in U.S. Patent No. 6,004,948. Cox-2 selective inhibitors that are useful in the subject method and compositions can include the compounds that are described in U.S. Patent Nos. 6,169,188, 6,020,343, 5,981,576 ((methylsulfonyl)phenyl furanones); U.S. Patent No. 6,222,048 (diaryl-2-(5H)-furanones); U.S. Patent No. 6,057,319 (3,4-diaryl-2-hydroxy-2,5-dihydrofurans); U.S. Patent No. 6,046,236 (carbocyclic sulfonamides); U.S. Patent Nos. 6,002,014 and 5,945,539 (oxazole derivatives); and U.S. Patent No. 6,359,182 (C-nitroso compounds).

[00231] Cyclooxygenase-2 selective inhibitors that are useful in the present invention can be supplied by any source as long as the cyclooxygenase-2-selective inhibitor is pharmaceutically acceptable. Cyclooxygenase-2-selective inhibitors can be isolated and purified from natural sources or can be synthesized. Cyclooxygenase-2-selective inhibitors should be of a quality and purity that is conventional in the trade for use in pharmaceutical products.

[00232] Anti-survival agents include c-Met antibodies and anti-integrin agents, such as anti-integrin antibodies.

Diagnostic Methods of Use

[00233] The c-Met antibodies may be used to detect c-Met in a biological sample if *in vitro* or *in vivo*. The c-Met antibodies may be used in a conventional immunoassay, including, without limitation, an ELISA, an RIA, FACS, tissue immunohistochemistry, Western blot, or immunoprecipitation. The c-Met antibodies of the invention may be used to detect c-Met from humans. In another embodiment, the c-Met antibodies may be used to detect c-Met from Old World primates such as cynomolgus and rhesus monkeys, chimpanzees and apes.

[00234] The invention provides a method for detecting c-Met in a biological sample comprising contacting a biological sample with an c-Met antibody of the invention and detecting the bound antibody bound to c-Met, to detect the c-Met in the biological sample. In one embodiment, the c-Met antibody is directly labeled with a detectable label. In another embodiment, the c-Met antibody (the first antibody) is unlabeled and a second antibody or other molecule that can bind the c-Met antibody and is labeled. As is well known to one of skill in the art, a second antibody is chosen that is able to specifically bind the specific species and class of the first antibody. For example, if the c-Met antibody is a human IgG, then the secondary antibody may be an anti-human-IgG. Other molecules that can bind to many antibodies include, without limitation, Protein A and Protein G, both of which are available commercially, e.g., Amersham Pharmacia Biotech. Suitable labels for the antibody or secondary detection antibodies have been disclosed *supra*, and include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, magnetic agents and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; an example of a magnetic agent includes gadolinium; and examples of suitable radioactive material include ^{125}I, ^{131}I, ^{35}S or ^{3}H.

[00235] In an alternative embodiment, c-Met can be assayed in a biological sample by a competition immunoassay utilizing c-Met standards labeled with a detectable substance and an unlabeled c-Met antibody. In this assay, the biological sample, the labeled c-Met standards, and the c-Met antibody are combined and the amount of labeled c-Met standard bound to the unlabeled antibody is determined. The amount of c-Met in the biological sample is inversely proportional to the amount of labeled c-Met standard bound to the c-Met antibody.

[00236] One may use the immunoassays disclosed above for a number of purposes. In one embodiment, the c-Met antibodies may be used to detect c-Met present in cells in cell culture. In a preferred embodiment, the c-Met antibodies may be used to determine the level of tyrosine phosphorylation, tyrosine autophosphorylation of c-

Met, and/or the amount of c-Met on the cell surface after treatment of the cells with various compounds. This method can be used to test compounds that may be used to activate or inhibit c-Met, or result in a redistribution of c-Met on the cell surface or intracellularly. In this method, one sample of cells is treated with a test compound for a period of time while another sample is left untreated. If tyrosine autophosphorylation is to be measured, the cells are lysed and tyrosine phosphorylation of the c-Met is measured using an immunoassay described above or as described in Example III, which uses an ELISA. If the total level of c-Met is to be measured, the cells are lysed and the total c-Met level is measured using one of the immunoassays described above. The level of cell-surface c-Met may be determined using antibodies of the invention staining tissue culture cells following fixation of the cells. Standard practices of those skilled in the art allow fluorescence-activated cell sorting (FACS) to be used with a secondary detection antibody to determine the amount of binding of the primary (c-Met) antibody to the cell surface. Cells may also be permeabilized with detergents or toxins to allow the penetration of normally impermeant antibodies to now label intracellular sites where c-Met is localized.

[00237] A preferred immunoassay for determining c-Met tyrosine phosphorylation or for measuring total c-Met levels is an ELISA or Western blot. If only the cell surface level of c-Met is to be measured, the cells are not lysed, and the cell surface levels of c-Met are measured using one of the immunoassays described above (e.g., FACS). A preferred immunoassay for determining cell surface levels of c-Met includes the steps of labeling exclusively the cell surface proteins with a detectable label, such as biotin or ^{125}I, immunoprecipitating a detergent-soluble fraction of the cells containing integral membrane proteins with a c-Met antibody, and then detecting the fraction of total c-Met containing the detectable label. Another preferred immunoassay for determining the localization of c-Met, e.g., cell surface levels is by using immunofluorescence or immunohistochemistry. Methods such as ELISA, RIA, Western blot, immunohistochemistry, cell surface labeling of integral membrane proteins and immunoprecipitation are well known in the art. See, e.g., Harlow and Lane, *supra*. In addition, the immunoassays may be scaled up for high throughput screening in order to test a large number of compounds for either activation or inhibition of c-Met.

[00238] The c-Met antibodies of the invention may also be used to determine the levels of c-Met in a tissue or in cells derived from the tissue. In a preferred embodiment, the tissue is a diseased tissue. In a more preferred embodiment, the tissue is a tumor or a biopsy thereof. In a preferred embodiment of the method, a tissue or a biopsy thereof is excised from a patient. The tissue or biopsy is then used in an immunoassay to determine, e.g., c-Met levels, cell surface levels of c-Met, levels of tyrosine phosphorylation of c-Met, or localization of c-Met by the methods discussed above. The method can be used to determine if a tumor expresses c-Met at a high level.

[00239] The above-described diagnostic method can be used to determine whether a tumor expresses high levels of c-Met, which may he indicative that the tumor will respond well to treatment with c-Met antibody. The diagnostic method may also be used to determine whether a tumor is potentially cancerous, if it expresses high levels of c-Met, or benign, if it expresses low levels of c-Met. Further, the diagnostic method may also be used to determine whether treatment with c-Met antibody (see below) is causing a tumor to express lower levels of c-Met and/or to express lower levels of tyrosine autophosphorylation, and thus can be used to determine whether the treatment is successful. In general, a method to determine whether an c-Met antibody decreases tyrosine phosphorylation comprises the steps of measuring the level of tyrosine phosphorylation in a cell or tissue of interest, incubating the cell or tissue with an c-Met antibody or antigen-binding portion thereof, then re-measuring the level of tyrosine phosphorylation in the cell or tissue. The tyrosine phosphorylation of c-Met or of another protein(s) may be measured. The diagnostic method may also be used to determine whether a tissue or cell is not expressing high enough levels of c-Met or high enough levels of activated c-Met, which may be the case for individuals with dwarfism, osteoporosis, or diabetes. A diagnosis that levels of c-Met or active c-Met are too low could be used for treatment with activating c-Met antibodies, HGF or other therapeutic agents for increasing c-Met levels or activity.

[00240] The antibodies of the present invention may also be used *in vivo* to localize tissues and organs that express c-Met. In a preferred embodiment, the c-Met antibodies can be used to localize c-Met expressing tumors. The advantage of the c-Met antibodies of the present invention is that they will not generate an immune response upon administration. The method comprises the steps of administering an c-

Met antibody or a pharmaceutical composition thereof to a patient in need of such a diagnostic test and subjecting the patient to imaging analysis determine the location of the c-Met expressing tissues. Imaging analysis is well known in the medical art, and includes, without limitation, x-ray analysis, magnetic resonance imaging (MRI), or computed tomography (CE). In another embodiment of the method, a biopsy is obtained from the patient to determine whether the tissue of interest expresses c-Met rather than subjecting the patient to imaging analysis. In a preferred embodiment, the c-Met antibodies may be labeled with a detectable agent that can be imaged in a patient. For example, the antibody may be labeled with a contrast agent, such as barium, which can be used for x-ray analysis, or a magnetic contrast agent, such as a gadolinium chelate, which can be used for MRI or CE. Other labeling agents include, without limitation, radioisotopes, such as ^{99}Tc. In another embodiment, the c-Met antibody will be unlabeled and will be imaged by administering a second antibody or other molecule that is detectable and that can bind the c-Met antibody.

Therapeutic Methods of Use

[00241] In another embodiment, the invention provides a method for inhibiting c-Met activity by administering a c-Met antibody to a patient in need thereof. Any of the types of antibodies described herein may be used therapeutically. In a preferred embodiment, the c-Met antibody is a human, chimeric, or humanized antibody. In another preferred embodiment, the c-Met is human and the patient is a human patient. Alternatively, the patient may be a mammal that expresses a c-Met that the c-Met antibody cross-reacts with. The antibody may be administered to a nonhuman mammal expressing a c-Met with which the antibody cross-reacts (i. e. a primate, or a cynomolgus or rhesus monkey) for veterinary purposes or as an animal model of human disease. Such animal models may be useful for evaluating the therapeutic efficacy of antibodies of this invention.

[00242] As used herein, the term "a disorder in which c-Met activity is detrimental" is intended to include diseases and other disorders in which the presence of high levels of c-Met in a subject suffering from the disorder has been shown to be or is suspected of being either responsible for the pathophysiology of the disorder or a factor that contributes to a worsening of the disorder. Accordingly, a disorder in

which high levels of c-Met activity is detrimental is a disorder in which inhibition of c-Met activity is expected to alleviate the symptoms and/or progression of the disorder. Such disorders may be evidenced, for example, by an increase in the levels of c-Met on the cell surface or in increased tyrosine autophosphorylation of c-Met in the affected cells or tissues of a subject suffering from the disorder. The increase in c-Met levels may be detected, for example, using a c-Met antibody as described above.

[00243] In a preferred embodiment, a c-Met antibody may be administered to a patient who has a c-Met-expressing tumor. A tumor may be a solid tumor or may be a non-solid tumor, such as a lymphoma. In a more preferred embodiment, an anti-IGF-antibody may be administered to a patient who has a c-Met-expressing tumor that is cancerous. In an even more preferred embodiment, the c-Met antibody is administered to a patient who has a tumor of the lung, breast, prostate, or colon. In a highly preferred embodiment, the method causes the tumor not to increase in weight or volume or to decrease in weight or volume. In another embodiment, the method causes the c-Met on the tumor to be internalized. In a preferred embodiment, the antibody is selected from PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, and PGIA-05-A1, or comprises a heavy chain, light chain or antigen-binding region thereof.

[00244] In another preferred embodiment, a c-Met antibody may be administered to a patient who expresses inappropriately high levels of HGF. It is known in the art that high level expression of HGF can lead to a variety of common cancers. In a more preferred embodiment, the c-Met antibody is administered to a patient with prostate cancer, glioma, or fibrosarcoma. In an even more preferred embodiment, the method

causes the cancer to stop proliferating abnormally, or not to increase in weight or volume or to decrease in weight or volume.

[00245] In one embodiment, said method relates to the treatment of cancer such as brain, squamous cell, bladder, gastric, pancreatic, breast, head, neck, esophageal, prostate, colorectal, lung, renal, kidney, ovarian, gynecological or thyroid cancer. Patients that can be treated with a compounds of the invention according to the methods of this invention include, for example, patients that have been diagnosed as having lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors (e.g., uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina or carcinoma of the vulva), Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system (e.g., cancer of the thyroid, parathyroid or adrenal glands), sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter (e.g., renal cell carcinoma, carcinoma of the renal pelvis), or neoplasms of the central nervous system (e.g., primary CNS lymphoma, spinal axis tumors, brain stem gliomas or pituitary adenomas).

[00246] The antibody may be administered once, but more preferably is administered multiple times. The antibody may be administered from three times daily to once every six months. The administering may be on a schedule such as three times daily, twice daily, once daily, once every two days, once every three days, once weekly, once every two weeks, once every month, once every two months, once every three months and once every six months. The antibody may be administered via an oral, mucosal, buccal, intranasal, inhalable, intravenous, subcutaneous, intramuscular, parenteral, intratumor, or topical route. The antibody may be administered at a site distant from the site of the tumor. The antibody may also be administered continuously via a minipump. The antibody may be administered once, at least twice or for at least the period of time until the condition is treated, palliated, or cured. The antibody generally will be administered for as long as the tumor is present provided that the antibody causes the tumor or cancer to stop growing or to decrease in weight

or volume. The antibody will generally be administered as part of a pharmaceutical composition as described *supra*. The dosage of antibody will generally be in the range of 0.1-100 mg/kg, more preferably 0.5-50 mg/kg, more preferably 1-20 mg/kg, and even more preferably 1-10 mg/kg. The serum concentration of the antibody may be measured by any method known in the art. The antibody may also be administered prophylactically in order to prevent a cancer or tumor from occurring. This may be especially useful in patients that have a "high normal" level of HGF because these patients have been shown to have a higher risk of developing common cancers. See Rosen et al., *supra*.

[00247] In another aspect, the c-Met antibody may be co-administered with other therapeutic agents, such as antineoplastic drugs or molecules, to a patient who has a hyperproliferative disorder, such as cancer or a tumor. In one aspect, the invention relates to a method for the treatment of the hyperproliferative disorder in a mammal comprising administering to said mammal a therapeutically effective amount of a compound of the invention in combination with an anti-tumor agent selected from the group consisting of, but not limited to, mitotic inhibitors, alkylating agents, anti-metabolites, intercalating agents, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, kinase inhibitors, matrix metalloprotease inhibitors, genetic therapeutics and anti androgens. In a more preferred embodiment, the antibody may be administered with an antineoplastic agent, such as Adriamycin or taxol. In another preferred embodiment, the antibody or combination therapy is administered along with radiotherapy, chemotherapy, photodynamic therapy, surgery, or other immunotherapy. In yet another preferred embodiment, the antibody will be administered with another antibody. For example, the c-Met antibody may be administered with an antibody or other agent that is known to inhibit tumor or cancer cell proliferation, e.g., an antibody or agent that inhibits erbB2 receptor, EGF-R, CD20, or VEGF.

[00248] Co-administration of the antibody with an additional therapeutic agent (combination therapy) encompasses administering a pharmaceutical composition comprising the c-Met antibody and the additional therapeutic agent and administering two or more separate pharmaceutical compositions, one comprising the c-Met antibody and the other(s) comprising the additional therapeutic agent(s). Further,

although co-administration or combination therapy generally means that the antibody and additional therapeutic agents are administered at the same time as one another, it also encompasses instances in which the antibody and additional therapeutic agents are administered at different times. For instance, the antibody may be administered once every three days, while the additional therapeutic agent is administered once daily. Alternatively, the antibody may be administered prior to or subsequent to treatment of the disorder with the additional therapeutic agent. Similarly, administration of the c-Met antibody may be administered prior to or subsequent to other therapy, such as radiotherapy, chemotherapy, photodynamic therapy, surgery, or other immunotherapy

[00249] The antibody and one or more additional therapeutic agents (the combination therapy) may be administered once, twice or at least the period of time until the condition is treated, palliated or cured. Preferably, the combination therapy is administered multiple times. The combination therapy may be administered from three times daily to once every six months. The administering may be on a schedule such as three times daily, twice daily, once daily, once every two days, once every three days, once weekly, once every two weeks, once every month, once every two months, once every three months and once every six months, or may be administered continuously via a minipump. The combination therapy may be administered via an oral, mucosal, buccal, intranasal, inhalable, intravenous, subcutaneous, intramuscular, parenteral, intratumor or topical route. The combination therapy may be administered at a site distant from the site of the tumor. The combination therapy generally will be administered for as long as the tumor is present provided that the antibody causes the tumor or cancer to stop growing or to decrease in weight or volume.

[00250] In a still further embodiment, the c-Met antibody is labeled with a radiolabel, an immunotoxin, or a toxin, or is a fusion protein comprising a toxic peptide. The c-Met antibody or c-Met antibody fusion protein directs the radiolabel, immunotoxin, toxin, or toxic peptide to the c-Met-expressing tumor or cancer cell. In a preferred embodiment, the radiolabel, immunotoxin, toxin, or toxic peptide is internalized after the c-Met antibody binds to the c-Met on the surface of the tumor or cancer cell.

[00251] In another aspect, the c-Met antibody may be used therapeutically to induce apoptosis of specific cells in a patient in need thereof. In many cases, the cells

targeted for apoptosis are cancerous or tumor cells. Thus, in a preferred embodiment, the invention provides a method of inducing apoptosis by administering a therapeutically effective amount of a c-Met antibody to a patient in need thereof. In a preferred embodiment, the antibody is selected from PGIA-01-A1, PGIA-01-A2, PGIA-01-A3, PGIA-01-A4, PGIA-01-A5, PGIA-01-A6, PGIA-01-A7, PGIA-01-A8, PGIA-01-A9, PGIA-01-A10, PGIA-01-A11, PGIA-01-A12, PGIA-01-B1, PGIA-01-B2, PGIA-02-A1, PGIA-02-A2, PGIA-02-A3, PGIA-02-A4, PGIA-02-A5, PGIA-02-A6, PGIA-02-A7, PGIA-02-A8, PGIA-02-A9, PGIA-02-A10, PGIA-02-A11, PGIA-02-A12, PGIA-02-B1, PGIA-03-A1, PGIA-03-A2, PGIA-03-A3, PGIA-03-A4, PGIA-03-A5, PGIA-03-A6, PGIA-03-A7, PGIA-03-A8, PGIA-03-A9, PGIA-03-A10, PGIA-03-A11, PGIA-03-A12, PGIA-03-B1, PGIA-03-B2, PGIA-03-B3, PGIA-03-B4, PGIA-03-B5, PGIA-03-B6, PGIA-03-B7, PGIA-03-B8, PGIA-04-A1, PGIA-04-A2, PGIA-04-A3, PGIA-04-A4, PGIA-04-A5, PGIA-04-A6, PGIA-04-A7, PGIA-04-A8, PGIA-04-A9, PGIA-04-A10, PGIA-04-A11, PGIA-04-A12, and PGIA-05-A1, or comprises a heavy chain, light chain, or antigen-binding region thereof.

[00252] In another aspect, the c-Met antibody may be used to treat noncancerous states in which high levels of HGF and/or c-Met have been associated with the noncancerous state or disease. In one embodiment, the method comprises the step of administering a c-Met antibody to a patient who has a noncancerous pathological state caused or exacerbated by high levels of HGF and/or c-Met levels or activity. In a preferred embodiment, the noncancerous pathological state is psoriasis, atherosclerosis, smooth muscle restenosis of blood vessels or inappropriate microvascular proliferation, such as that found as a complication of diabetes, especially of the eye. In a more preferred embodiment, the c-Met antibody slows the progress of the noncancerous pathological state. In a more preferred embodiment, the c-Met antibody stops or reverses, at least in part, the noncancerous pathological state.

[00253] The antibodies of the present would also be useful in the treatment or prevention of ophthalmic diseases, for example glaucoma, retinitis, retinopathies (e.g., diabetic retinopathy), uveitis, ocular photophobia, macular degeneration (e.g., age related macular degeneration, wet-type macular degeneration, and dry-type macular degeneration) and of inflammation and pain associated with acute injury to the eye tissue. The compounds would be further useful in treatment or prevention of postsurgical ophthalmic pain and inflammation.

[00254] In another aspect, the invention provides a method of administering an activating c-Met antibody to a patient in need thereof. In one embodiment, the activating antibody or pharmaceutical composition is administered to a patient in need thereof in an amount effective to increase c-Met activity. In a more preferred embodiment, the activating antibody is able to restore normal c-Met activity. In another preferred embodiment, the activating antibody may be administered to a patient who has small stature, neuropathy, a decrease in muscle mass or osteoporosis. In another preferred embodiment, the activating antibody may be administered with one or more other factors that increase cell proliferation, prevent apoptosis, or increase c-Met activity. Such factors include growth factors such as HGF, and/or analogues of HGF that activate c-Met.

Gene Therapy

[00255] The nucleic acid molecules of the instant invention may be administered to a patient in need thereof via gene therapy. The therapy may be either *in vivo* or ex viva. In a preferred embodiment, nucleic acid molecules encoding both a heavy chain and a light chain are administered to a patient. In a more preferred embodiment, the nucleic acid molecules are administered such that they are stably integrated into the chromosome of B cells because these cells are specialized for producing antibodies. In a preferred embodiment, precursor B cells are transfected or infected ex vivo and retransplanted into a patient in need thereof. In another embodiment, precursor B cells or other cells are infected *in vivo* using a virus known to infect the cell type of interest. Typical vectors used for gene therapy include liposomes, plasmids, or viral vectors, such as retroviruses, adenoviruses, and adeno associated viruses. After infection either in viva or ex vivo, levels of antibody expression may be monitored by taking a sample from the treated patient and using any immunoassay known in the art and discussed herein.

[00256] In a preferred embodiment, the gene therapy method comprises the steps of administering an effective amount of an isolated nucleic acid molecule encoding the heavy chain or the antigen-binding portion thereof of the human antibody or portion thereof and expressing the nucleic acid molecule. In another embodiment, the gene therapy method comprises the steps of administering an effective amount of an

isolated nucleic acid molecule encoding the light chain or the antigen-binding portion thereof of the human antibody or portion thereof and expressing the nucleic acid molecule. In a more preferred method, the gene therapy method comprises the steps of administering an effective amount of an isolated nucleic acid molecule encoding the heavy chain or the antigen binding portion thereof of the human antibody or portion thereof and an effective amount of an isolated nucleic acid molecule encoding the light chain or the antigen-binding portion thereof of the human antibody or portion thereof and expressing the nucleic acid molecules. The gene therapy method may also comprise the step of administering another anti cancer agent, such as taxol, tamoxifen, 5-FU, Adriamycin or CP-358,774.

[00257] In order that this invention may be better understood, the following examples are set forth. These examples are for purposes of illustration only and are not to be construed as limiting the scope of the invention in any manner.

EXAMPLES

EXAMPLE 1

Selection of c-Met Binding ScFv's

[00258] An scFv phagemid library, which is an expanded version of the $1.38x10^{10}$ library described by Vaughan *et al.* (Nature Biotech. (1996) 14: 309-314) was used to select antibodies specific for human c-Met. Two selection methodologies were employed; panning selections and soluble selections.

[00259] For the panning method, soluble c-Met fusion protein (at 10 μg/ml in phosphate buffered saline (PBS)) or control fusion protein (at 10 μg/ml in PBS) was coated onto wells of a microtitre plate overnight at 4°C. Wells were washed in PBS and blocked for 1 hour at 37°C in MPBS (3% milk powder in PBS). Purified phage (10^{12} transducing units (tu)) was blocked for 1 hour in a final volume of 10 μl of 3% MPBS. Blocked phage was added to blocked control fusion protein wells and incubated for 1 hour. The blocked and deselected phage was then transferred to the blocked wells that were coated with the c-Met fusion protein and were incubated for an additional hour. Wells were washed 5 times with PBST (PBS containing 0.1% v/v Tween 20), then 5 times with PBS. Bound phage particles were eluted and used to

infect 10 ml of exponentially growing *E. coli* TG1. Infected cells were grown in 2TY broth for 1 hour at 37°C, then spread onto 2TYAG plates and incubated overnight at 30°C. Colonies were scraped off the plates into 10 ml 2TY broth and 15% glycerol added for storage at -70°C.

[00260] Glycerol stock cultures from the first round panning selection were superinfected with helper phage and rescued to give scFv antibody-expressing phage particles for the second round of panning. A total of three rounds of panning were carried out in this way for isolation of antibody-expressing phage particles specific for human c-Met.

[00261] For the soluble selection method, biotinylated human c-Met fusion protein at a final concentration of 50 nM was used with scFv phagemid library, as described above. Purified scFv phage (10^{12} tu) in 1 ml 3% MPBS were blocked for 30 minutes, then biotinylated antigen was added and incubated at room temperature for 1 hour. Phage/antigen was added to 50 µl of Dynal M280 Streptavidin magnetic beads that had been blocked for 1 hour at 37°C in 1 ml of 3% MPBS and incubated for a further 15 minutes at room temperature. Beads were captured using a magnetic rack and washed 5x in 1 ml of 3% MPBS/ 0.1% (v/v) Tween 20 followed by 2 washes in PBS. After the last PBS wash, beads were resuspended in 100 µl PBS and used to infect 5 ml of exponentially growing *E. coli* TG-1 cells. Infected cells were incubated for 1 hour at 37°C (30 minutes stationary, 30 minutes shaking at 250 rpm), then spread on 2TYAG plates and incubated overnight at 30°C. Output colonies were scraped off the plates and phage rescued as described above. Two further rounds of soluble selection were performed as described above.

[00262] The nomenclature used to refer to the single-chain (scFv) antibodies was "PGIA" followed by the microtiter plate number and well number. For Example the c-Met scFv antibody from plate 1, well A1 was designated "PGIA-01-A1".

EXAMPLE 2

c-Met Protein Expression and Purification

Conversion to IgG

[00263] Clones were converted into the IgG format as described below. Reformatting involves the subcloning of the VH domain from the scFv into a vector containing the human heavy chain constant domains, and regulatory elements for the appropriate expression in mammalian cells. Similarly, the VL domain is subcloned into an expression vector containing the human light chain constant domain (lambda or kappa class) along with the appropriate regulatory elements

[00264] The nucleic acid sequence encoding the appropriate domain from the scFv clone was amplified, followed by restriction enzyme digestion and ligation into the appropriate expression vector. Heavy Chain (IgG1 constant domain) were cloned into pEU1, Light Chain (lambda class) were cloned into pEU4, and Light Chain (kappa class) were cloned into pEU3 (Persic, L. et al., *Gene* 187:9-18 (1997))

Site Directed Mutagenesis

[00265] Prior to reformatting, it was observed that several scFvs (including PGIA-03-A11) contained an internal BstEII restriction site within the VH domain that would interfere with cloning of the VH into the IgG1 heavy chain vector. The internal restriction site was removed by Quikchange™ (Invitrogen)site-directed mutagenesis using the method as described in the kit. Oligos MUTF QFRVTM (CAGGGCAGGGTCACAATGGCCAG SEQ ID NO:121) and MUTR QFRVTM (CTGGCCATTGTGACCCTGCCCTG SEQ ID NO:122) were designed to remove the restriction site but maintaining the same amino acid sequence. Sequencing was carried out to ensure that the site had been mutated correctly.

VH/VL cloning PCR

[00266] Once all sequences were checked for the absence of restriction sites, the nucleic acid sequence encoding the VH and VL domains were amplified in separate PCR reactions.

[00267] 100ul PCR reactions were set up for each VH and VL domain using 50ul 2x PCR master mix, 5ul forward primer (@10uM), 5ul reverse primer (@10uM), and

40ul water. Primers were allocated according to the scFv sequence, and are shown in Table 4

TABLE 4

IgG Clone	scFv Clone	VH Forward primer	VH reverse primer	VL forward primer	VL reverse primer
11978	PGIA-1-A8	AF14	H-Link	AF42	AF23
11994	PGIA-3-A9	AF11	H-Link	AF42	AF23
12075	PGIA-3-A11	AF18	H-Link	AF31	AF28
12119	PGIA-5-A1	RH55	H-Link	AF42	AF23
12123	PGIA-3-B2	AF11	H-Link	AF21	RH62
12133	PGIA-4-A5	AF11	H-Link	AF42	AF47
12136	PGIA-4-A8	AF11	H-Link	AF40	AF29

[00268] A single bacterial colony containing the appropriate nucleic acid encoding the scFv in pCANTAB6 (WO 94/13804, Figures 19 and 20) was picked into each PCR reaction and the sample was amplified using the following parameters: 94°C for 5 minutes, 94°C for 1min., 30 cycles of 55°C for 1 min. and 72°C 1min., and 72°C 5 min.

Digestion

[00269] The PCR products were cleaned up using a QIAquick™ 8-well purification kit (Catalog # 28144, Qiagen, Valencia CA) according to the manufacturer's directions. A 25ul aliquot of the amplified VH PCR products was digested with BssHII and BstEII. A 25ul aliquot of the amplified VL PCR products was digested with ApaLI and PacI.

[00270] The digested VH and VL PCR products were cleaned up using a QIAquick purification kit.

Ligation and Transformation

[00271] An aliquot of the cleaned up, digested PCR product was ligated into the appropriate vector digested with the same restriction enzymes. VH domains were ligated into pMON27816 (pEU1), and VL domains were ligated into either pMON27820 (pEU3) or pMON27819 (pEU4), depending on light chain class (Persic et al., *Gene* 187: 9-18, 1997). A portion of each of the ligation reactions was transformed into previously prepared chemically competent DH5α *E. coli* by heat shock and grown overnight on 2xTY agar plates containing Ampicillin.

Screening

[00272] Individual ampicillin resistant colonies were picked into liquid 2TY media (containing Ampicillin) in a 96-well plate and grown overnight. Once cultured, the colonies were screened by PCR to determine whether the vectors contained the appropriate domains. VH-containing plasmids were screened using the primers, PECSEQ1 and p95, and VL-containing plasmids were screened using the primers, PECSEQ1 and p156.

[00273] Colonies containing inserts were analyzed by DNA sequencing using the same primers as used for the screening PCR.

[00274] Table 5 shows the oligonucleotide primers used to amplify the VH and VL domains.

TABLE 5

Oligo Name	Oligo Sequence (5'-3')	Function of Oligo
AF11	CTCTCCACAGGCGCGCACTCCCAGGTGCAGCTG CAGGAG SEQ ID NO:123	VH forward PCR cloning primer
AF14	CTCTCCACAGGCGCGCACTCCGAGGTGCAGCTG TTGGAG SEQ ID NO:124	VH forward PCR cloning primer
AF18	CTCTCCACAGGCGCGCACTCCCAGGT(GC)CAG CTGGTGCA SEQ ID NO:125	VH forward PCR cloning primer
RH55	CTCTCCACAGGCGCGCACTCCCAGCTGCAGCTG CAGGAGTCGGGC SEQ ID NO:126	VH forward PCR cloning primer
HLINK	ACCGCCAGAGCCACCTCCGCC SEQ ID NO:127	VH reverse PCR cloning primer
AF21	CTCCACAGGCGTGCACTCCCAGGCTGTGCTGAC TCAGCC SEQ ID NO:128	VL forward PCR cloning primer
AF31	CTCTCCACAGGCGTGCACTCCCAGTCTGTGCTG ACTCAGCC SEQ ID NO:129	VL forward PCR cloning primer
AF40	CCACAGGCGTGCACTCCTCCTATGAGCTGACTC AG SEQ ID NO:130	VL forward PCR cloning primer
AF42	CTCCACAGGCGTGCACTCCAATTTTATGCTGAC TCAG SEQ ID NO:131	VL forward PCR cloning primer
AF23	CTATTCCTTAATTAAGTTAGATCTATTCTGACT CACCTAGGACGGTCAGCTTGGTCCCTC SEQ ID NO:132	VL reverse PCR cloning primer
AF47	CTATTCCTTAATTAAGTTAGATCTATTCTGACT CACCTAGGACGGTGACCTTGGTCCC SEQ ID NO:133	VL reverse PCR cloning primer
AF28	CTATTCCTTAATTAAGTTAGATCTATTCTGACT CACCTAGGACGGTCAGCTTGGTCCCACT SEQ ID NO:134	VL reverse PCR cloning primer
AF29	CTATTCCTTAATTAAGTTAGATCTATTCTGACT CACCTAGGACGGTGACCTTGGTCCCAGT SEQ ID NO:135	VL reverse PCR cloning primer
RH62	CTATTCCTTAATTAAGTTAGATCTATTCTGACT CACCTAGGACGGTGAGCTGGGTCCC SEQ ID NO:136	VL reverse PCR cloning primer
PECSEQ1	GCAGGCTTGAGGTCTGGAC SEQ ID NO:137	VH/VL forward screening Primer
P156	TAATTATAGCAAGGAGACCAAGAAG SEQ ID NO:138	VL reverse screening primer
P95	CAGAGGTGCTCTTGGAGGAGGGTGC SEQ ID NO:139	VH reverse screening primer

[00275] After the scFvs were converted to IgGs or Fabs a different naming convention was used. Table 6 shows the correlation between the scFv nomenclature and the corresponding IgG or Fab nomenclature. For example scFv "PGIA-01-A2" was converted to an IgG designated "12118 IgG" and the Fab designated "12118 Fab".

Table 6

scFv Clone ID	IgG and Fab	scFv Clone ID	IgG and Fab	scFv Clone ID	IgG and Fab
PGIA-1-A1	*	PGIA-2-A8	12072	PGIA-3-B4	12077
PGIA-1-A2	12118	PGIA-2-A9	11980	PGIA-3-B5	12128
PGIA-1-A3	11987	PGIA-2-A10	11981	PGIA-3-B6♦	12078
PGIA-1-A4	*	PGIA-2-A11	11991	PGIA-3-B6♦	12124
PGIA-1-A5	12122	PGIA-2-A12	12073	PGIA-3-B7♦	12079
PGIA-1-A6	12129	PGIA-2-B1	12074	PGIA-3-B7♦	12125
PGIA-1-A7	*	PGIA-3-A1	11982	PGIA-3-B8	12080
PGIA-1-A8	11978	PGIA-3-A2	12130	PGIA-4-A1	12131
PGIA-1-A9	12126	PGIA-3-A3	11983	PGIA-4-A2	*
PGIA-1-A10	*	PGIA-3-A4	11984	PGIA-4-A3	12132
PGIA-1-A11	*	PGIA-3-A5	11992	PGIA-4-A4	12139
PGIA-1-A12	*	PGIA-3-A6	11985	PGIA-4-A5	12133
PGIA-1-B1	11988	PGIA-3-A7	12127	PGIA-4-A6	12134
PGIA--1-B2	*	PGIA-3-A8	11993	PGIA-4-A7	12135
PGIA-2-A1	11989	PGIA-3-A9	11994	PGIA-4-A8	12136
PGIA-2-A2	12068	PGIA-3-A10	11995	PGIA-4-A9	12137
PGIA-2-A3	11990	PGIA-3-A11	12075	PGIA-4-A10	12138
PGIA-2-A4	12069	PGIA-3-A12	11997	PGIA-4-A11	12120
PGIA-2-A5	12070	PGIA-3-B1	11986	PGIA-4-A12	12121
PGIA-2-A6	11979	PGIA-3-B2	12123	PGIA-5-A1	12119
PGIA-2-A7	12071	PGIA-3-B3	12076	PGIA-3-B4	12077

* = not converted to IgG and Fab
♦ = two isolates selected

Expression of c-Met MAb

[00276] Expression of the functional heavy chain gene cassette was driven by the GV promoter and terminated by the SV40 poly adenylation signal. The GV promoter is a synthetic promoter comprised of five repeats of the yeast Gal4 upstream activation sequence plus a minimal CMV promoter (Carey, M. et al., Nature 345 (1990), 361-364). The vector also contained the dhfr expression cassette from pSV2dhfr. Chinese hamster ovary (CHO/GV) cells transformed to express a chimeric transactivator (GV) derived from the fusion of the yeast Gal4 DNA binding domain and the VP16 transactivation domain (Carey, M. et al., Nature 345 (1990), 361-364) were transfected simultaneously with heavy-chain and light chain expression vectors using Lipofectamine 2000 (Gibco) according to the manufacturers instructions. Cell

were grown at 37°C, 5% CO_2 in IMDM (Invitrogen) + 10% FBS (Invitrogen) + 1x HT supplement (Invitrogen) for forty-eight hours after transfection and then the cells were placed under selection by removing hypoxanthine and thymidine from the media (IMDM + 10% dialyzed FBS (Invitrogen)). After 10 days the pool of cells was cloned in 96-well plates and after 14 days in culture the 96-well plates were screened and the highest expressing clones were expanded. Expression was done in roller bottles by plating one confluent T75 flask into one 1700 cm^2 roller bottle containing 400 ml of IMDM + 10% dialyzed FBS media.

Purification of c-Met MAb

[00277] Purification of c-Met immunoglobulins was accomplished by affinity chromatography utilizing 1 ml Amersham Fast Flow recombinant protein A columns. The columns were equilibrated with 20 mls of GIBCO PBS pH 7.4(#12388-013) at 1 ml per minute. Conditioned media containing anti c-Met IgG was 0.2 micron filtered then applied to the equilibrated column at 0.5 ml per minute. Unbound protein was washed from the column with 60 ml of PBS at 1 ml per minute. The IgG was eluted with 20 ml of 0.1 M glycine plus 0.15 M NaCl pH 2.8 at 1 ml per minute. The eluate was collected into 2 ml of 1 M Tris Cl pH 8.3 with stirring. Amicon Centriprep YM-30 filtration units were used to concentrate the eluates (22 ml) to approximately 1.5 ml. The concentrates were dialyzed in Pierce 10K MWCO Slide-A-lyzer cassettes versus 2 X 1 L of PBS. Following dialysis the IgG was passed through a 0.2 micron filter, aliquoted and stored frozen at –80 C. IgG was characterized by reducing and non-reducing SDS PAGE, size exclusion chromatography and quantitated by absorbance at 280 nm using a calculated extinction coefficient of 1.45 OD units equals 1 mg/ml. A subset was additionally characterized by N-terminal amino acid sequencing and amino acid compositional analysis.

c-Met Fab production

[00278] Fabs of selected c-Met IgG were generated and purified by papain cleavage and protein A separation utilizing the Pierce ImmunoPure Fab Kit # 44885 following the protocols supplied with the kit. Fabs were characterized by reducing

and non-reducing SDS PAGE and size exclusion chromatography. For the c-Met 11978 Fab which bound to protein A after papain cleavage, anion exchange chromatography on a TosoHaas Q-5PW HPLC column of dimensions 7.5mm X 7.5CM, particle size 10μ, catalog #18257 was utilized for the purification process. The separation was achieved using a binary buffer system, with the primary buffer 20mM Tris, pH9.0 the counter ion buffer was 20mM Tris, pH9.0, 1M NaCl. The c-Met 11978 Fab was buffer exchanged into 20mM Tris, pH9.0 then injected onto the anion exchange column. The column was then washed with 30ml of primary buffer. The c-Met 11978 Fab was purified by a linear gradient of 0-60% counter ion buffer over 40 minutes. The c-Met 11978 Fab eluted at 0.3M NaCl. The purity was >95%.

EXAMPLE 3

Expression and Purification of Recombinant NK4 Proteins

[00279] The CHO DG44 cell line was transfected with pPHA27965 [A cDNA encoding NK4-6His was synthesized by PCR as described (Kuba et al., *BBRC* 279: 846, 2000) and inserted by standard cloning techniques into pCMV1 (pEU1) with the CMV promoter (Stinski et al., *J Virol* 46: 1-14, 1983) substituted for the elongation factor promoter]. Forty-eight hours after transfection the cells were placed under selection and expanded. After 7-10 days the cells were then amplified with methotrexate. Once amplified the CHO DG44/pPHA27965 cells were cloned, screened and expanded. The highest expressing clone was further expanded and the protein was expressed in roller bottles.

Purification of Recombinant NK4-6His

[00280] Conditioned medium harvested from the roller bottle cultures of NK4-6His, was pooled and adjusted to 50mM Hepes (pH 6.8). Gross particulates were removed by centrifuging at 28,000 g for 1 hour, and the supernatant fractions were adjusted to 0.02% sodium azide. The NK4-6His was purified by a two-stage chromatographic procedure. The first stage was nickel agarose affinity purification. The NK4-6His was eluted by a linear gradient of imidazole from 5 – 250mM. The nickel agarose elution fractions containing NK4-6His were determined by SDS-

PAGE and the relevant fractions were pooled. The first stage pool was then dialyzed against 20mM sodium citrate (pH 6.5), containing 0.01% Tween-80. The adjusted pool was then loaded onto heparin agarose resin. The heparin agarose resin was eluted by a linear sodium chloride gradient from 0 – 1.8M. The NK4-6His eluted from the resin at approximately 1.3 M sodium chloride. The finished sample was > 99% pure by analytical GPC and SDS-PAGE and had a molecular weight of 55kDa.

EXAMPLE 4

c-Met Ligand Competition ELISA

ELISA Plate Preparation

[00281] 96-well Fluoronunc plates were coated with 50ul of 0.5ug/ml c-Met/Fc Chimera (R&D Systems, Minneapolis MN, catalog # 358-MT-100) in phosphate buffered saline (PBS) and the plates were incubated overnight at room temperature. Wells were washed three times with washing buffer (PBS + 0.1% Tween 20), blotting the plates on paper towels between each wash. Nonspecific binding in the wells was blocked by the addition of 250ul of blocking buffer (3.0% milk (Carnation) in PBS) to each well and incubated at room temperature for two hours.

ELISA for detecting inhibition of binding of biotin-HGF to c-Met/Fc Chimera

[00282] The c-Met antibodies were diluted in reagent buffer (PBS, 0.5% BSA, 0.05% Tween-20) and titrations were performed in 96 well polypropylene plates. Biotinylated HGF (0.4 ug/ml) (R&D Systems, biotinylated with Pierce #21335 as per manufacturer's instructions) was added to each well. 50ul of the dilutions were transferred into the Fluoronunc plates containing human c-Met-Fc fusion protein (R&D Systems, #) and the plates were incubated for two hours at room temperature. The plates were washed three times with wash buffer and blotted onto paper towels. 50ul of europium-labeled Streptavidin (Wallac Perkin Elmer) diluted 1:1000 in Delfia assay buffer (Wallac Perkin Elmer) was added per well and the plates were incubated for one hour at room temperature. The plates were washed seven times with Delfia wash buffer (Tris buffered saline (TBS) supplemented with 0.1% Tween-20) and

blotted onto paper towels. 100ul Delfia enhancer solution (Wallac Perkin Elmer) was added to each well and the plates incubated for 5 minutes on a plate shaker at room temperature. Plates were read on a fluorescence plate reader and analyzed using GraphPad Prism software (GraphPad Software, San Diego, CA).

[00283] Table 7 shows the IC50 values for the c-Met IgG antibodies and Fab fragments. C-Met antibodies 1A3.3.13 (#HB-11894, ATCC Hybridoma) and 5D5.11.6 (#HB-11895, ATCC Hybridoma) were used as positive controls. MOPC-21 (#M-7894, Sigma) was used as an IgG isotype control and HB-94 (#HB-94, ATCC Hybridoma) was converted into a Fab fragment and used as a Fab isotype control. NK4-Elastase is a kringle1 to kringle 4 fragment resulting from digesting intact HGF purified from S-114 cells with elastase (Date et al., *FEBS Lett.* 420:1-6 (1977).

TABLE 7

Sample ID	IgG (n=2) IC50 (nM)	Fab (n=2) IC50 (nM)
11978	0.84	65.9, >125
11994	0.58	24.57
12075	2.55	>125
12119	0.64	10.65
12123	0.50	
12133	0.58	
12136	1.00	
11986	0.52	80.00
1A3.3.13 (+mAb control)	0.50	6.83
5D5.11.6 (+mAb control)	>125	9.72
MOPC-21 (-mAb control)		
HB94 (-Fab control)		>125
NK4-Elastase		900, 551.4
NK4-His		>125

EXAMPLE 5

Inhibition of HGF-induced Cellular Proliferation by c-Met Antibodies

[00284] c-Met antibodies in the IgG and Fab formats were assayed to evaluate their ability to inhibit HGF-induced DNA synthesis. Human mammary epithelial 184B5 cells (ATCC #CRL-8799) were plated at a cell density of 2.5×10^4/well into 96-well flat bottom cell culture cluster plates (Corning #3596) in 80µl per well of starvation

media containing RPMI-1640 (Gibco, #21870-084) supplemented with 2mM L-glutamine (Gibco #25030-081), 10 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (Gibco #15630-080; Hepes), 50 U/ml penicillin-streptomycin (Gibco #15070-063), and 0.1% protease-free bovine serum albumin (Equitech-Bio, Kerrville, TX). Plates were incubated at 37°C/5% CO_2 for 24 hours. 10µl of assay media or 10µl of 10X the final concentration for the test monoclonal antibodies was added per well. Plates were incubated at 37 °C/5% CO_2 for 30 minutes. 10 µl of 10X the final concentration (130 pM) of rhHGF (R&D Systems #294-HGN/CF) diluted in assay media was added to each well and incubated 16-20 hours at 37 °C/5% CO_2. During the last 2 hrs of this incubation 10µl of diluted BrdU labeling solution, 10µM final concentration (Roche, #1647229, Cell Proliferation Elisa, BrdU, colorimetric) was added to all wells. The media was decanted by inverting the plates and blotting gently onto a paper towel. Plates were then dried at 60°C for 1 hour. Fix denaturing solution (Roche, #1647229) was then added at 200µl per well and incubated 30-45 minutes at room temperature. Plates were decanted again onto a paper towel and 200µl of Dulbecco's PBS (Gibco, #14040-117) containing 2% BSA (Equitech-Bio) was added to each well to block for 30 minutes at room temperature. PBS was decanted and 100µl of anti-BrdU-POD (monoclonal antibody, clone BMG 6H8, Fab fragment conjugated with peroxidase) was added per well and incubated for 90 minutes at room temperature. The antibody conjugate was removed by decanting and tapping the plate onto a paper towel. The plates were rinsed 3x with 275µl/well washing solution (Roche, #1647229). 100µl/well of TMB substrate solution (tetramethyl-benzidine, Roche, #1647229) was added to the wells and incubated at room temperature for 5-30 minutes. 25µl of 1M H_2SO_4 (VWR, #VW3232-1) was added and incubated approximately 1 minute with thorough mixing to stop further plate development. The optical density was measured on an ELISA plate reader (Bio-Rad, Model #3550) at 450 nm against a reference wavelength 595 nm.

[00285] Table 8 indicates the ability of several IgG antibodies, Fab fragments of these antibodies, or compounds to inhibit HGF dependent proliferation of these cells under assay conditions.

TABLE 8

Sample ID	IgG (n=3)	Fab (n=2)
11978	+	-
11994	++	+
12075	+	-
12119	+	+
12123	+	-
12133	++	+
12136	+	+
1A3.3.13	++	+
MOPC-21 IgG	-	
anti-HGF Ab	+++++	
5D5.11.6	+++	+
HB94		-
NK4-Elastase	+++	
NK4-His	+++	
Media alone	-	-
ovalbumin	-	

*Number of + = Degree of Inhibition
- = No Inhibition

EXAMPLE 6

Enhancement of c-Met IgGs and Fabs on c-Met Tyrosine Phosphorylation

[00286] To evaluate whether addition of IgG or Fab versions of c-Met antibodies could enhance the phosphorylation of c-Met protein kinase domain HCT-116 human colon carcinoma cells (ATCC #CCL-247) were plated at a cell density of 5xE4/well into six well tissue culture clusters with 2ml per well of McCoy's medium (Gibco, #16600-082) supplemented with 2mM L-glutamine (Gibco, #25030-081), 20 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (Gibco, #15630-080; Hepes), and 10% fetal bovine serum (heat-inactivated; HyClone, #SH30070.03). Cells were incubated at 37°C/5%CO_2 until 70-80% confluent, and the culture media was replaced with 2ml of the above medium containing 0.2% bovine serum albumin (Equitech-Bio, protease-free, Kerrville, TX) instead of FBS. After overnight incubation, the starvation media was replaced with 2.5 ml per well of fresh starvation media pre-warmed to 37°C, and containing 10nM or 100nM of selected ligands or test

monoclonal antibodies. Dishes were incubated at 37°C in a circulating water bath for 10 minutes, the media was aspirated, dishes were placed on ice-water, and the cell monolayer was washed three times with 2ml per well of ice-cold Dulbecco's PBS (Gibco #14040-117). All subsequent operations were conducted at 4°C. Cells were removed from the dishes by addition of 0.3ml per well of cell lysis buffer. Cell lysis buffer is 1% (v/v) Nonidet P40 (Boehringer Mannheim #1332473), 0.15M NaCl, 25mM Tris-HCl, (pH 7.5) containing 10% (v/v) glycerol, 5mM EDTA, 2mM sodium fluoride, and a 1/100 dilution of stock protease (Sigma P-8340), and phosphatase (Sigma P-2850 and P-5726) inhibitor cocktails. Dishes were shaken in lysis buffer for 5min, and the contents of each well containing 1.17xE6 cell equivalents were transferred to microfuge tubes, vortexed briefly, and allowed to stand for 30 minutes. The lysate was clarified by centrifuging at 10,000g for 20 min (Sorvall Legend RT) at 5°C, and 2ul of the supernatant fraction was assayed for total protein by the method of Bradford (Bradford, Anal. Biochem. 72:248-254, 1976) using the dye reagent obtained from BioRad (# 500-0006) and bovine serum albumin as a protein standard. Equivalent volumes of the supernatant fraction (with a known amount of protein) were mixed with SDS-PAGE sample buffer (Novex) containing 5% (v/v) 2-mercaptoethanol, heated at 90°C for 5 minutes, and analyzed by SDS-PAGE on 4-12% Nu-PAGE Bis-Tris gels (Novex # NP0322) in MOPS buffer (Novex # NP0001). For Western blot analysis, proteins were transferred to nitrocellulose (Schleicher and Schuell, BA-85) overnight at 4°C at 0.2A in Nu-PAGE transfer buffer (Novex # NP0006-1) containing 10% (v/v) methanol. Membranes were blocked for 1 hour at room temperature with blotto (5% (w/v) non-fat dry milk (Carnation), 25mM Tris-HCl (pH 7.5), 0.15M NaCl, 0.1% (v/v) Tween20, 0.01% thimerosol), then incubated for three hours at room temperature in 1/5000 dilution of rabbit c-Met (Santa Cruz Biotechnology, #sc-161) in 25mM Tris-HCl, (pH 7.5), 0.15M NaCl, 0.05% (v/v) Tween-20 (TBST) supplemented with 5% bovine serum albumin. Alternatively, that portion of c-Met containing phosphotyrosine within the kinase domain activation loop was determined by incubation of membranes prepared in an identical manner as above in 1/5000 dilution of rabbit anti-pY c-Met IgG (Biosource, #44-888). Peroxidase-conjugated secondary antibody (Jackson Immunoresearch, #111-035-144) was applied at 1/7500 dilution for 45 minutes at room temperature, and then the membranes were washed twice for 30 minutes with TBS containing 0.2% Tween-20,

and developed with Supersignal (Pierce #34080) as per manufacturer's instructions. Exposures were captured for 10 or 20 seconds on Bio-Max MR-1 film (Sigma, Z35, 039-7) and band intensity was quantitated by laser densitometry (Molecular Dynamics, Personal Densitometer SI) and analyzed using ImageQuant software. Band intensity was normalized for the total protein contained in each sample, and the fold increase versus control (no addition) signal intensity was determined. Figure 4 shows that both HGF and multiple c-Met antibodies enhanced the phosphorylation of the c-Met kinase domain over this time period under these conditions, whereas isotype control irrelevant monoclonal antibody (MOPC-21) or irrelevant ligand (IGF-1) did not significantly enhance the endogenous level of phosphotyrosine-containing c-Met. The total amount of c-Met protein subjected to analysis (detected as both the 170kDa precursor and 145kDa mature versions of the receptor) was found to be comparable in each analyzed sample.

EXAMPLE 7

c-Met Phosphorylation ELISA

[00287] The ability of c-Met monoclonal antibodies to induce tyrosine phosphorylation of c-Met upon binding was also determined using an ELISA format. For this purpose, 96 well plates (VWR, #62409-002) were coated overnight at 4°C with 100ng per well of mouse c-Met monoclonal antibody (1A3.3.13 IgG1; ATCC #HB-11894) or isotype-control monoclonal antibody (Sigma, M-5284) in 50ul of 50mM sodium borate (pH 8.3; Pierce, #28384). Residual capture antibody was removed and unreacted binding sites were blocked by addition of 180ul per well of Superblock-TBS (Pierce, #37535). After standing five minutes at room temperature, the blocking step was repeated, then the wells were rinsed twice with Tris-buffered saline (TBS, Sigma, T-5912) supplemented with 0.05% Tween-20 (Sigma P-1379) (TBST), and once with distilled water. Dilutions of cell lysates were added to wells in a final volume of 50ul of TBS containing 0.1% Tween-20 and 0.2% BSA (Equitech-Bio, 30% solution, protease-free, Kerrville, TX) (ELISA buffer), and capture of c-Met protein was allowed to proceed overnight at 4°C. Wells were rinsed twice with TBST and once with distilled water, then 50ul/well of a 1/2000 dilution of rabbit anti-phosphotyrosine c-Met (Biosource, #44-888) was added to each well in

ELISA buffer and incubated for one hour at room temperature. Wells were washed twice with TBST and once with distilled water. 100ul per well of a 1/20,000 dilution of horseradish peroxidase-conjugated goat anti-rabbit IgG-- (Jackson Immunoresearch, #111-035-144) in ELISA buffer was added and the plates incubated for one hour at room temperature. Wells were rinsed three times with TBST and once with distilled water, then developed by addition of 100ul per well of TMB solution (Sigma, T-4444). Development was allowed proceed at room temperature for 2-5 minutes, then the signal was quenched by addition of 100ul per well of 7.7% (v/v) phosphoric acid. Optical density was then recorded at 450nm versus 595nm reference wavelength using an ELISA reader (Bio-Rad). The results shown in Figure 4 on duplicate samples obtained with this ELISA assay were comparable to those observed with Western blotting analysis, and confirmed the ability of the tested c-Met monoclonal antibodies to enhance tyrosine phosphorylation of c-Met when compared to MOPC-21 control isotype antibody or untreated control samples.

EXAMPLE 8

Scatter Assay

[00288] The agonistic potential of the c-Met antibodies in the absence of HGF as well as the antagonistic potential of c-Met antibodies in the presence of HGF was evaluated using a scatter assay. DU-145 cells were plated at 1000 cells/well in 96-well Perkin Elmer view plates (catalog no. 6005182), or 2500 cells/well in 48-well Greiner Cellstar plates (catalog no. 677180), in RPMI-1640 Media supplemented with 10% Fetal Bovine Serum and Gibco non-essential amino acids. After the cells were allowed to settle down for two hours in a humidified cell culture chamber at 37 C and 5% CO2, HGF and/or inhibitors are added to the wells in triplicates. The cells were kept in the cell culture chamber above for 48 to 72 hours. Subsequently, the cells were fixed with 2% paraformaldehyde (Electron Microscopy Sciences, catalog no. 15713-S). Cytoplasmic and nucleic areas of the cells were stained with propidium iodide (Molecular Probes, catalog no. P-3566) and Hoechst dye, respectively. Levels of scattering were measured in a Cellomics ArrayScan II, and expressed as mean object areas.

[00289] Table 9 shows the agonistic potential of several c-Met antibodies and Fab fragments and compounds in the absence of HGF as well as the antagonistic potential of c-Met antibodies and compounds in the presence of HGF.

TABLE 9

	IgG		Fab	
Sample ID	**Agonist (alone)**	**Antagonist (w/ 30 pM HGF)**	**Agonist (alone)**	**Antagonist (w/ 30 pM HGF)**
11978	459+/-130	372+/-87		
11994-50	272+/-30*	294+/-27*	738+/-145	404+/-19
11986			501+/-82	557+/-201
12075	318+/-98	289+/-61		
12119	285+/-15	293+/-20		
12123	234+/-0.007	226+/-2		
12133	241+/-23	230+/-38		
12136	249+/-27*	296+/-64*		
1A3.3.13	305+/-66	254+/-24	597+/-45	400 (n=1)
5D5.11.6	239+/-16	241+/-13	632+/-74	592+/-76
HB94	365+/-38	199+/-14	592+/-84	478+/-91
NK4-Elastase	335+/-17	471+/-130	740+/-129	697+/-208
HGF		324+/-37		
media alone			685+/-445 (No HGF)	352+/-56

Cellomics measurement at 100 nM IgG or Fab except * at 50 nM.

The smaller the number, the more scattering.

EXAMPLE 9

Scratch Assay with c-Met Antibodies

[00290] To evaluate the ability of the c-Met IgG and Fab antibodies to inhibit recombinant human HGF (R&D Systems, # 249-HG)-induced cell motility a scratch assay was used that incorporated robotic-induced scratches. Visualization using a fluorogenic intracellular substrate, Vybrant CFDA (Molecular Probes, #V-12883) was used to maximize invasion visibility and produce images with a high signal/noise ratio. Analysis of the migration into the scratch area was performed using AnalySIS Software (Soft Imaging Systems, Lakewood CO).

Plate Setup

[00291] NCI H441 (ATCC #HTB-174) adenocarinoma cells from a 70-90% confluent T-162 cm^2 flask were washed with PBS and harvested with trypsin/EDTA. Released cells were suspended in 10 ml RPMI-1640 (Gibco, #11875-085) supplemented with 10% fetal bovine serum (Gibco, #26140-079) and dispensed into 48-well tissue culture plates containing 0.5 ml of RPMI-1640 supplemented with 10% fetal bovine serum. Scratches were induced in confluent monolayers by a pipette tip using a Biomek 2001 robot (Beckman Coulter, Fullerton CA), producing a single scratch per well. A fresh tip was used for each row. The wounded cell monolayers were gently washed twice with 0.5 ml RPMI-1640, once with PBS, and then treated with 0.5 ml per well RPMI-1640 with 0.1% BSA (Sigma, #A8327) containing test antibodies or controls at concentrations ranging from 0.1 - 30 ug/ml. After a 20 minute pre-incubation, 50ul of HGF (final concentration = 225 pM) was added to each well and the plates were incubated 20-24 hours at 37°C/5%CO_2.

Plate Staining and Analysis

[00292] Vybrant Dye Solution was prepared by dissolving 90ul of DMSO in one vial of dye and then transferring to 37 ml of HBSS (Gibco, #14025-092). Media from the wells was aspirated and 0.5 ml of Vybrant Dye solution was added. After 30 minutes incubation at 37°C/5%CO_2, the dye solution was replaced with 0.5 ml HBSS. After 20minutes at 37°C/5%CO_2 image analysis was performed. Cell monolayers were then fixed with 1% freshly prepared formaldehyde in PBS.

[00293] Fluorescence images were captured on a Nikon TE300 inverted fluorescence microscope with a 2X objective and a FITC filter pack. The microscope has a motorized stage controlled by AnalySIS well navigator software (Soft Imaging System GMBH) and was used to automate the data collection. Analysis of the area of the scratch was done using this software. Area of the scratch was reported in um^2. Data was processed and plotted using Excel Software. When replicates were tested, SEM was used for error bars.

[00294] Table 10 Displays data of the inhibition of the c-Met IgG antibodies and Fab fragments compared with that observed with 1A3.3.13 and 5D5.11.6 IgGs and Fabs, or recombinant NK4.

TABLE 10

Sample ID	Scratch Assay*	(Cell Motility) (n=3)
	IgG	Fab
11978	+	+/-
11994	++	+/-
12075	+/-	+/-
12119	++	+/-
12123	+	+/-
12133	++	+/- (2/3); +(1/3)
12136	++	+/-
1A3.3.13	+	+/-
5D5.11.6	++	+/-
NK4-His	++	NR
MOPC-21	+/-	+/-
HB94	+/-	+/-

* Inhibition > 1A3 IgG (++)
Inhibition < 1A3 IgG (+)
No Activity (+/-)
NR---Not Relevant

EXAMPLE 10

Biacore Assay

[00295] The binding properties (on-rate, off-rate and affinity) of c-Met monoclonal antibodies (IgG or Fab versions) with human c-Met extracellular domain was determined using surface plasmon resonance, or BIAcore, technology. For the binding studies with IgG, a low density (<1ng/mm2) of c-Met-Fc (R&D Systems, #358-MT-

100/CF) containing 5.1 biotin per c-Met molecule (prepared with Pierce #21335 as per manufacturer's instructions) was captured onto a SA chip precoated with Streptavidin (BIAcore Inc.). A streptavidin flow cell without adsorbed c-Met-Fc was used as a control cell for non-specific binding. The antibody sample to be analyzed was prepared in HEPES buffer (0.15M NaCl, 10mM HEPES, 3.4mM EDTA, 0.005% surfactant P-20, pH 7.4) to form a set of solutions varied in concentration from 0.78nM to 100nM. The HEPES buffer used as the running solution was set at a flow rate of 50ul/min. Each sample solution was injected over the two flow cells for three minutes, followed by 5 minutes of dissociation. The flow cells were then regenerated with 4.5M $MgCl_2$ for one minute to remove the bound antibody for the next cycle of binding study. The net sensorgrams (subtraction of sensorgrams from the negative control flow cell as well as that from the buffer blank) obtained for each set of samples were processed simultaneously in a global fitting using a bivalent binding model of the BIAevaluation software program equipped with the system. The on-rate (k_a), off-rate (k_d) and binding affinity (K_D) were determined from the fitting with K_D equal to k_d/k_a.

For the binding study of Fab fragments derived from antibodies of the invention, a high density (>2ng/mm^2) of protein A was first immobilized covalently onto a CM5 sensorchip using EDC/NHS amine coupling chemistry [. The flow cell containing c-Met-Fc captured by the protein A was used as the positive control while a flow cell containing only protein A was used as the negative control. The Fab sample to be analyzed was as above for antibodies to form a set of solutions with concentration ranged from 3.9nM to 500nM. The HEPES buffer used as the running solution was set at a flow rate of 50ul/min. For each cycle of binding study, low density (<1ng/mm^2) of c-Met-Fc was captured first onto the positive flow cell. Each sample solution was then injected over the two flow cells (one negative and one positive in series) for three minutes followed by 5 minutes of dissociation. The flow cells were then regenerated with 4.5M $MgCl_2$ for one minute to remove the bound c-Met-Fc/Fab complexes for the next cycle of binding. The net sensorgrams (subtraction of sensorgrams from the negative control flow cell as well as that from the buffer blank) obtained from the set of samples were fitted simultaneously in a global fitting using a Langmuir 1:1 binding model of the BIAevaluation program equipped with the system.

The on-rate (k_a), off-rate (k_d) and binding affinity (K_D) were determined from the fitting with K_D equal to k_d/k_a.

[00296] Tables 11 and 12 show the binding kinetics of several c-Met IgG antibodies and Fab fragments respectively.

TABLE 11

c-Met IgGs

Sample ID	on-rate(1/sM)	off-rate(1/s)	KD(nM)
11978	ND	ND	ND
11994	9.06E+04	7.59E-04	8.4
12075	1.53E+04	8.45E-03	552
12119	8.60E+04	1.12E-03	13
12123	3.38E+05	3.29E-03	9.7
12133	9.89E+04	5.98E-04	6
12136	2.94E+05	2.29E-04	0.8
1A3.3.13	2.10E+05	2.89E-04	1.4
5D5.11.6	6.88E+04	4.06E-04	5.9

TABLE 12

c-Met Fabs

Sample ID	on-rate(1/sM)	off-rate(1/s)	Kd(nM)
11994	3.83E+05	5.28E-03	13.8
12133	2.80E+05	2.45E-03	8.8
12136	1.68E+05	1.01E-03	6
1A3.3.13	4.97E+05	3.13E-03	6.3
5D5.11.6	1.26E+05	1.29E-04	1